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CŒLIAC DISEASE*

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RECENT EVIDENCE of etiological factors, as well as changes in the method of management of cœliac disease, has prompted a review of the so-called idiopathic form of this disease.

The cœliac syndrome in children has challenged a great many workers since Samuel Gee's[1] classical description. The etiological factors which have been proposed are also numerous. At one time it was thought to be due to a particular intestinal infection but none was ever discovered. Dietary factors have been suggested as the cause, the harmful influence of complex sugars and poor absorption of fat being the chief ones, while allergies and various other causes have been reported. Certain intestinal parasites can produce a similar picture, as well as mechanical defects in the gastrointestinal tract. About 1937 Dr. Dorothy Andersen[2] and Dr. Kenneth Blackfan separated fibrocystic disease of the pancreas from idiopathic cœliac disease and stimulated further interest in the etiology of this latter disease.

The clinical picture in typical cœliac disease is probably well known. The wasting of the child's body and failure to thrive, associated with steatorrhœa, has become standard knowledge found in most textbooks of children's diseases. Cœliac disease is a chronic disturbance of nutrition resulting from poor absorption of fat and other nutrients. There is alternating looseness of the bowels and at times constipation. The number of stools varies tremendously from a single large voluminous undigested stool, to frequent, frothy, foul-smelling stools showing excessive fat. The abdomen is usually distended with gas and undigested food. It has a soft doughy feel due to the loose contents. The abdominal wall becomes very thin because of loss of subcutaneous fat and muscle tissue. Examination of the gastrointestinal tract by x-rays shows barium in clumps in the intestinal lumen, probably due to excessive mucus content. There is loss of appetite and loss of, or stationary, weight. In some cases there is absence of subcutaneous fat followed by marked wasting of the limbs, particularly the buttocks, and the groins and axillary folds show wrinkled skin. The face may be full and have a normal appearance. If the disease continues there is marked retardation of growth, and deficiency signs and symptoms may appear. Radiological examination reveals bony growth to be delayed as shown by the centres of ossification[3] and also by transverse growth lines in the long bones. Crises may develop in which profuse watery diarrhœa may result in dehydration and marked electrolyte loss, and is often associated with an infection. Clubbing of the fingers appears fairly early in the severe cases and disappears with cure. It is a rough index of the degree of control of these patients. Anæmia is often present and the hair may be sparse. The child may have abdominal cramps; the extremities are usually cold; the patient is depressed and is either irritable or lethargic. Puberty may be delayed in prolonged cases. The disease may persist into adult life.[4]

The dentition is often delayed but the teeth usually remain quite good and free from caries. In a series of 50 children with cœliac disease between the ages of three and twelve years, for whom a careful dental examination was carried out at the Faculty of Dentistry, University of Toronto, it was found that, generally speaking, children with cœliac disease are "caries immune", and saliva tests showed "caries immunity". This is possibly due to the high protein, low sugar diet maintained by these children or to delayed growth.

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Three types of onset have been recognized in this disease. A few infants have a tendency to diarrhœa from birth which gradually goes on to the classical picture. The usual onset is between six months and two years, although it may occasionally start later in childhood. Approximately 50% of the children have a sudden onset associated with infection. Such infection may be enteral, such as dysentery, or parenteral, more commonly associated with nasopharyngitis and its complications. These infants develop diarrhœa which persists with loose undigested stools. They may have vomiting. The other 50% of cases have an insidious onset with alternating loose stools and constipation associated with loss of appetite and loss of, or stationary, weight. In both types of onset there is increasing irritability. We have shown[5] that the onset is later in infants who have been breast-fed than in those who were artificially fed, and also that the onset is usually earlier in those cases in which there is no known infection, such cases tending to have a more insidious type of onset. Many infants have developed their first signs after weaning or with the addition of foods, other than milk feedings, to the diet. Occasionally a known food allergy has been reported to be associated with the onset. This has been observed by other authors including Kunstadter.[6]

TABLE I.

RELATION OF TYPE OF FEEDING TO AGE AT ONSET OF CŒLIAC SYNDROME

	Average age at onset (months)		
	Breast feeding		*Artificial feeding*
All cases	15.5		12.2
Duration of breast feeding: 1 - 3 mos.		13.0	
Duration of breast feeding: 3 - 6 mos.		14.7	
Duration of breast feeding: over 6 mos.		17.3	
Onset with infection	17.2		13.0
Onset with no known infection	13.7		10.8

There are no specific pathological changes. The pancreas is normal in contradistinction to cystic fibrosis of the pancreas in which, in addition to undigested stools, there is usually associated lung infection and an absence of pancreatic enzymes when an alkaline sample of pancreatic secretion is aspirated from the duodenum. The oral glucose tolerance curve is usually low, the average rise being only 20 mg. % whereas the normal is over 40 mg. %. This is probably due to poor absorption but may also be partly caused by delayed emptying time of the stomach. The intravenous glucose tolerance curve is normal. The xylose tolerance test is low as compared with normal children and cases of fibrocystic disease.[7] The vitamin A tolerance curve is low and delayed, indicating poor absorption, but is not as low as that in fibrocystic disease of the pancreas. Examination of the stools reveals an excess of fat. This can only be done accurately by proper fat balance studies. A cœliac child usually puts out an average of 10 g. or more of fat daily, whereas the normal stool contains less than four or five g. per day. The excess fat excretion is chiefly due to poor absorption. The saturated fatty acids are not absorbed as well as the unsaturated. A typical fat balance study in cœliac disease is shown in Table II in which a control period has a very low absorption of fat varying from 47 to 75% absorption followed by a more normal absorption when the patient is on a controlled diet (gluten-free diet). The percentage of fat absorption is shown in Table III on a diet containing saturated fat and a diet containing unsaturated fat. It will be noted that in active cœliac disease there is less fat absorption when the diet is composed chiefly of saturated fatty acid (such as butter-fat) than

TABLE II.

FAT BALANCE STUDIES—CŒLIAC DISEASE (ACTIVE)
PERCENTAGE FAT ABSORPTION (DAILY ESTIMATIONS)

Day	*1*	*2*	*3*	*4*	*5*	*6*	*7*
On normal diet	75.2	56.9	56 5	47.5	52.1	56.9	67.3
On gluten-free diet	84.1	—	83.8	84.4	89.0	87.5	—

TABLE III.

FAT ABSORPTION

	Percentage fat absorption	
	Saturated fat diet	*Unsaturated fat diet*
Cœliac disease—active	73	85
Cœliac disease—arrested	90	92
Cœliac disease—arrested	89	93
Fibrocystic disease	72	73

with unsaturated fat. In arrested cœliac disease there is less difference, but there is poor absorption of both saturated and unsaturated fat in fibrocystic disease.

ETIOLOGY

A study of the families of our cœliac-disease children has shown that there is a family tendency.[8] The number of siblings, parents and grandparents who suffered from cœliac disease is definitely greater (Table IV). This is further

TABLE IV.

INCIDENCE OF CŒLIAC SYNDROME AMONG RELATIVES OF CŒLIAC PATIENTS

	Total number	*Number affected*	*Incidence*
Cœliacs	104	104	1.00
Sibs	117	16	0.14
Parents	189	10	0.05
Grandparents	361	4	0.01

supported by the fact that in twins reported in the literature where the type of twinning was indicated, and in twins in our own study (Table V),[8] five sets of identical twins all had

TABLE V.

CŒLIAC SYNDROME IN ELEVEN SETS OF TWINS

	Uniovular	*Binovular*
Concordance	5	3
Discordance	0	3
Total	5	6

cœliac disease, while of six sets of non-identical twins only three sets showed the disease in both twins.

A notable advance in our knowledge of the etiology of this disease was made by Dutch physicians[9, 10] a few years ago, resulting from observations during the famine in the western Netherlands in 1944-45 when practically no wheat or rye was available. It was noted that cœliac children improved, especially if wheat and rye flour had been excluded. It was also noted that these patients could tolerate wheat starch, potato and rice. Other workers then found that wheat flour increased the excretion of saturated fatty acids but did not affect the absorption of unsaturated fatty acids. Thus, butterfat, which is mainly saturated fatty acid, was poorly tolerated by cœliac children. Sheldon[11] had previously shown that the exclusion of all starch from the diet increased fat absorption and that cœliac children improved rapidly, gained weight and were much happier. This was confirmed by Lowe.[12] Anderson *et al.*[13] have confirmed the fact that the gluten in wheat and rye flours is responsible for the interference with absorption. It is not completely known which part of the gluten is responsible for the effect, or what the mechanism is. It is possible that it results from an excessive excretion of mucus in the small intestine, resulting in increased motility and poor absorption of all food substances. The Dutch workers[9, 10] feel that gluten may be a factor in conditions other than cœliac disease, namely various forms of indigestion and also enteritis in infants and small children.

TABLE VI.

CHANGES ON GLUTEN-FREE DIET—FOUR WEEKS

	Weight	*General condition*	*Abdomen*	*Stools*
Improved	19	20	13	14
Unchanged	3	5	7	9
Worse	1	1	1	3
No follow-up	3	0	5	0

In order to test the gluten theory, which was reported at the International Pædiatric Conference in Zurich in 1950, a number of children have been placed on gluten-free diets. These were children who were suffering or had suffered from cœliac disease and who were in various stages of arrest. The object was to remove gluten and provide gluten-free starch to determine whether or not the starch had any ill effect. The period of observation was only 28 days, but the results seemed to be significant (Table VI). The girth of the abdomen, the character of the stools and the weight of the child were recorded at the beginning of the 28 days of observation and again at the end. It will be noted that there was improvement in the weight, general condition, girth of the abdomen and character of the stools in the majority of these children on such a routine.

Case History of T.B. (Fig. 1)

This infant progressed well from birth until the age of six months. Mixed cereal had been introduced at the age of two months; the stools remained reasonably normal un-

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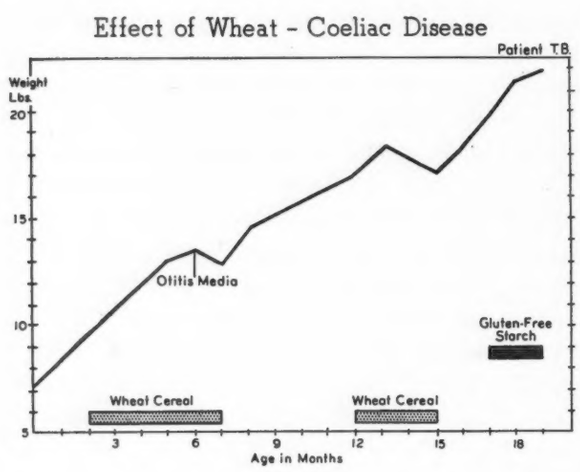


Fig. 1

til age six months when the child developed upper respiratory tract infection with a complicating otitis media. He then began to vomit and have loose stools, became dehydrated and required hospital admission. During this period fluids were administered and cereal was stopped. The stools returned to normal and the child continued to thrive on a milk feeding and other foods. Cereal containing wheat was again introduced at 12 months. The stools gradually became undigested and eventually loose, with loss of weight and early signs of cœliac disease. The child was then taken off the wheat cereal and again returned to normal. Gluten-free starch was administered for a period of eight weeks, during which time the condition continued to improve, the gluten-free starch having no unfavourable effect.

One cannot help but be impressed by the similarity of response to that in food allergy. The syndrome of milk intolerance is well known. In the majority of cases the reaction is rather violent but it can express itself in a subacute or chronic form with rather insidious signs and symptoms of indigestion. It is well known that allergies express themselves in different ways. In early infancy we have the exhibition of allergy in the form of eczema and food intolerance. Most of these cases seem to pass through this phase and possibly become desensitized to the offending substances, such as foods which were introduced early in the life of the child. The eczema usually clears but the child may then exhibit other forms of allergy such as asthma and hay fever. The fact that such a sequence is now being observed in some of our cœliac patients would make one suspicious that allergy may be the factor which is producing deleterious effects either in the intestinal wall or elsewhere in the body.

In our study allergy has been more prominent than one would expect in the general population. In clinical observation it was apparent that a few children did not respond as well as expected to a gluten-free diet. Careful study of our records and the history as given by the mothers showed that in a few cases other food substances were at fault, notably cow's milk, egg and orange. It was also found that a careful family history indicated a high incidence of allergy of some type. In 28 patients representing 25 families, 22 had a good direct and collateral family history of allergy. Seventeen gave a family history of major allergy and five patients suffered from a major allergy themselves. One must also take into consideration the fact that in young children major allergies may not yet have developed.

In an attempt to determine which foods were possibly causing the disturbance in some of our patients, Dr. C. Collins-Williams protein-skin-tested 28 cœliac patients with 47 of the common foods including wheat, barley, oats, rye and rice, and with the wheat protein fractions which were obtainable, namely gliadin, globulin, glutinen and proteose.[14] All tests were done by the intracutaneous method with the full realization of the limitations of skin tests with foods, particularly in gastrointestinal allergy. The 47 common foods were tested in the following concentrations—fruit, vegetables, meats and cereals except wheat and arrowroot in 1:500 dilution; egg, milk and wheat in 1:5000 dilution followed by a 1:1000 dilution if the weaker test was negative. All other foods were tested in the 1:1000 dilution. Twenty-three control patients, chosen at random on the basis of comparable age, were tested with the wheat fractions. In both groups a large number of positive reactions to wheat fractions were obtained.

Positive reactions to egg were obtained on seven occasions; to whole wheat on six occasions; to banana and pork on five; onion on four; salmon and celery on three; almond, walnut, pea, tomato, codfish, apricot, strawberry, grape, rice and bean on two; and 13 other foods on one occasion each. The wheat fractions gave positive reactions with globulin three times, glutinen twice and proteose once. Twenty-two cases of cœliac disease gave positive reactions with one or more foods and 10 gave positive reactions with wheat or one of the wheat fractions. Examination of these results shows there is very little correlation between the tests and the clinical results.

TREATMENT

For many years the treatment of this disease has been based on a high protein diet, eliminating as much fat as possible and reducing the content of sugar. Most patients have responded to such a routine provided that infection could be eliminated. However, a few patients still failed to thrive satisfactorily in spite of numerous adjustments of diet.

The present method of management of the severe cœliac patient starts with a correction of any dehydration by forcing clear fluids such as glucose drinks, and, if necessary, intravenous fluids and occasionally blood transfusion for anæmia.

The next stage of treatment consists of the introduction of simple protein foods such as, in the smaller children, protein milk (or boiled skim milk), scraped lean beef, ripe banana and jelly. New foods are then gradually introduced one at a time, with an interval of several days, in order to test the child, the diet gradually being built up to the following (depending upon the age of the child):

Instructions:

1. Eliminate all foods which contain any kind of wheat, oats, rye or barley (e.g. soups, gravy, ice cream, rusk, biscuit, toast).
2. Add to diet foods in the following list and increase amounts to satisfy appetite.
3. Gradually add sugar, corn syrup and honey.
4. Special recipes made from gluten-free starch (Ogilvie Company) should be tried (listed in appendix).
5. Add cautiously, potato, butter and fat-containing foods.

Diet:

7-8 a.m.—(1) Soft boiled, poached or scrambled egg, or one or two slices of crisp bacon. (2) One glass of milk (plain pasteurized—skimmed). (3) Special recipe bread (see appendix). (4) Juice of one orange diluted with water. (5) Rice cereal—when stools return to normal (pre-cooked, rice crispies, rice flakes).

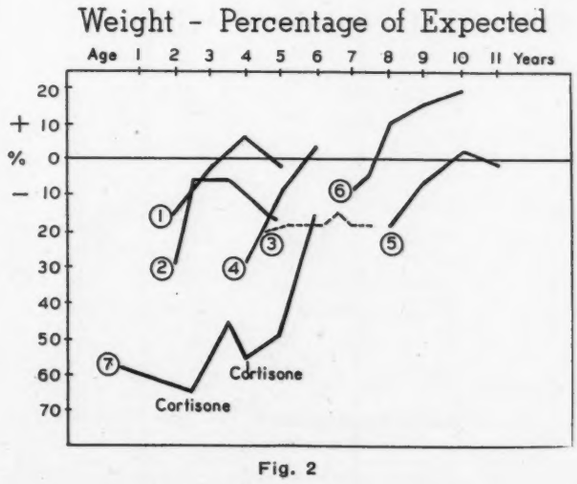
12-1 p.m.—(1) Lean steak, or roast beef, or lamb chop or roast lamb, or calves', beef or lambs' liver, or poultry, or boiled or baked fish, or soft boiled, poached or scrambled egg. No fat. (2) Occasionally boiled rice. (3) Two to three rounded tablespoons of one or two of the following vegetables without butter: spinach, swiss chard, beet tops, carrots, squash, vegetable marrow, yellow turnips, asparagus, stewed or canned tomatoes, stewed celery, stewed onions, string beans, lima beans, peas, cauliflower and young cabbage. (4) Dessert—two to six rounded tablespoons of stewed prunes, baked apple, apple sauce, stewed apricots, stewed pears, stewed peaches, or rice, or custard, junket, or gelatine pudding. The fruit desserts should be given 3 or 4 times a week, and cut-up bananas and oranges in particular should be included. (5) Special recipe cake or bread (see appendix).

6 p.m.—Same list as at lunch—one glass of skimmed milk.

Control of infection is most important, and suitable antibiotics should be administered in full doses and for a sufficiently long time to eradicate all sources of infection. This is particularly true of infections of the gastrointestinal tract and of the upper respiratory tract which contribute nasal secretion and swallowed mucus to an already impaired absorptive mechanism.

The administration of vitamin products is important. The dosage should be double the normal requirement of the child and given preferably in water-soluble form. While vitamins C and D are of most importance, the vitamin B complex and other factors are helpful in restoring the nutritional state. Occasionally intramuscular injections of crude liver extract and the vitamin B complex seem to assist the child in making an initial response to dietary therapy (1 c.c. daily for three weeks).

Careful periodic measurements of height, weight and abdominal girth are important in determining the degree of control of the cœliac disease. By comparing the actual stature of a child with the expected stature for their birth weight and length, one can chart progress. In Fig. 2, from the weight curves of several patients in various stages of the disease, it is obvious that the child's stature, when compared with the expected stature of the child, is very much below the ideal. However, with co-operation, the defective growth can be compensated for in part at least (Fig. 3). Periods of failure to maintain a prescribed diet are illustrated by patients 2 and 3 (Fig. 2).



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In Fig. 2 Patient 1 had been a known cœliac for a year. She had started at age six months. A severe upper respiratory tract infection had precipitated the acute episode, requiring blood transfusion and intravenous

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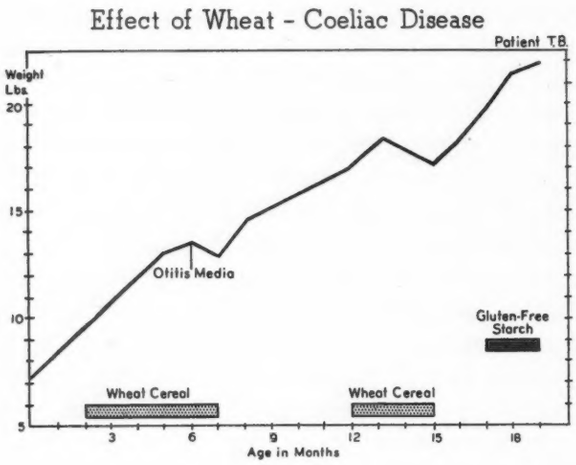

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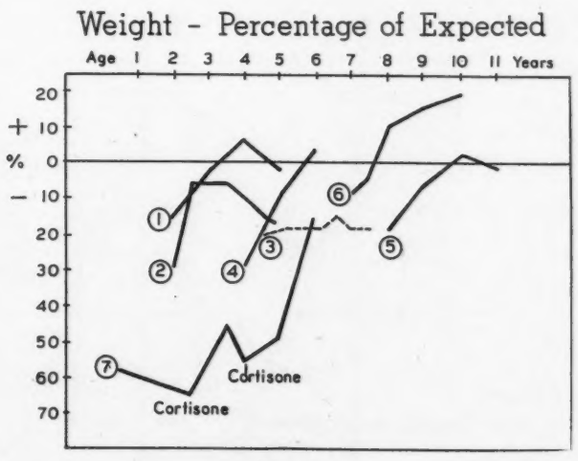

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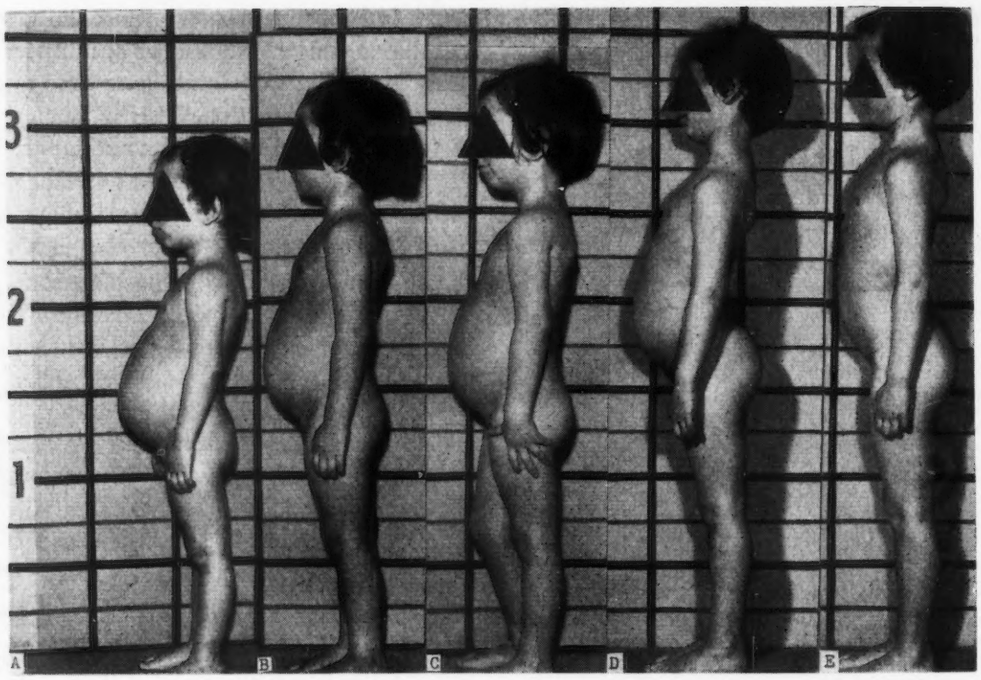

Fig. 3.—A—4 years 5 months; B—5 years 1 month; C—5 years 4 months; D—6 years 6 months; E—7 years 5 months.

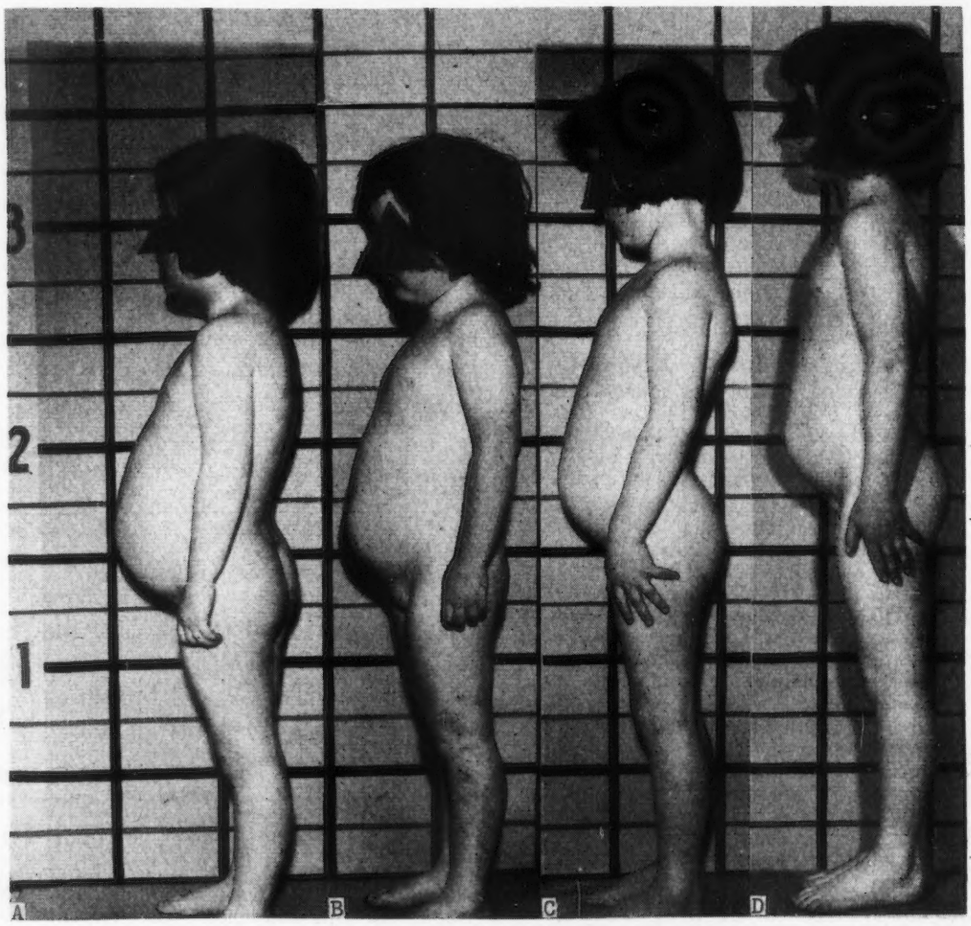

Fig. 4.—A—5 years 1 month; B—5 years 2 months; C—6 years; D—7 years 1 month.

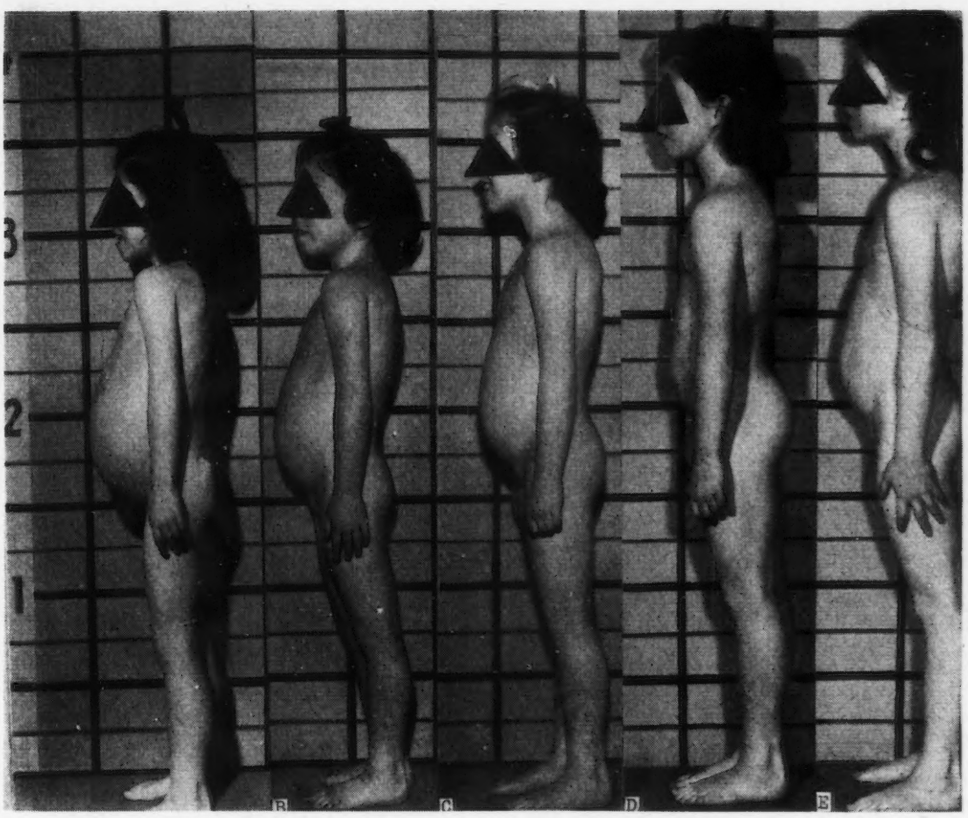

Fig. 5.—A—8 years; B—8 years 4 months; C—8 years 11 months; D—10 years; E—10 years 11 months.

fluids to restore hydration. With good co-operation there was an excellent response in clinical signs and symptoms and a satisfactory period of normal growth. The stools returned to normal, the child's vitality increased and she has had no further trouble other than periodic mild eczema and hives. There is a strong history of allergy in the family, and two cousins of the patient have had cœliac disease.

Patient 2 developed cœliac disease early in infancy, and lived in a foster home where there was poor co-operation and supervision. It is known that the child has been receiving some wheat in spite of being prescribed a suitable diet. It has been found that there are other cœliac and allergic relatives of this child. During a stay in hospital the child did well on a gluten-free diet but upon returning to the foster home her condition again became poor.

Patient 3 developed cœliac disease at the age of two years. She lives in a foster home where co-operation is poor and wheat is occasionally introduced into the diet. She has suffered from frequent respiratory infections, has abdominal cramps following eating of foods which contain wheat, and vomits whenever egg is given. Her weight gain has not been satisfactory.

In Patient 4 cœliac disease was diagnosed at age two years (Fig. 2). She developed a crisis following otitis media which resulted in intestinal ileus requiring emergency operation. Her condition improved dramatically with gluten-free diet but co-operation has been intermittent since. There is a strong history of allergy in the family, and a cousin has cœliac disease (Fig. 4).

Patient 5, now aged eight years, is a chronic cœliac from infancy. She was consuming a large amount of bread and was failing to grow. Wheat and egg caused abdominal pain. She suffered from many infections, and had marked clubbing of the fingers and a distended abdomen. At age six she developed asthma. There is a strong family history of allergy. The mother had cœliac disease in early life and now has asthma. After the introduction of a gluten-free and egg-free diet the child's physical condition altered. She became active physically, school work progressed, height and weight increased and her condition is now considered satisfactory (Fig. 5).

Patient 6 was maintained on a high protein diet for several years but there was slow gain. She was always pale and weak, with distended abdomen and undigested stools. There was a strong family history of allergy. The child has developed asthma. Since she went on a gluten-free diet she has grown well and has become a normal child with more energy.

Patient 7.—Rarely cœliac disease becomes chronic and does not appear to respond to usual methods. This patient illustrates the deleterious effect of starch as well as gluten and periodic infections in retarding the progress of the disease. There was also an element of poor co-operation on the part of the parents. The child became extremely wasted for a very long period of time and finally would not improve even with the elimination of gluten. Her weight was 60% below the expected weight for her age (Fig. 2). With the availability of ACTH, this was given a trial but was not beneficial; in fact, the child's condition deteriorated with each trial of ACTH. However, when the patient was given cortisone there was better retention of food, the child became happier, the appetite increased and progress rapidly became satisfactory (Fig. 2). In Fig. 6 the patient is shown following one of the crises (A), again after receiving the cortisone treatment (B), and subsequent progress, indicating rapid growth in height and weight (C, D, E). It was extremely difficult, however, to withdraw cortisone from this patient owing to a consistent return to undigested stools each time that therapy was stopped. However, it was gradually reduced and she is now able to tolerate most foods, except gluten,

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and although the abdomen is still prominent and her stature much below the normal for her age, her general condition has been improving markedly.

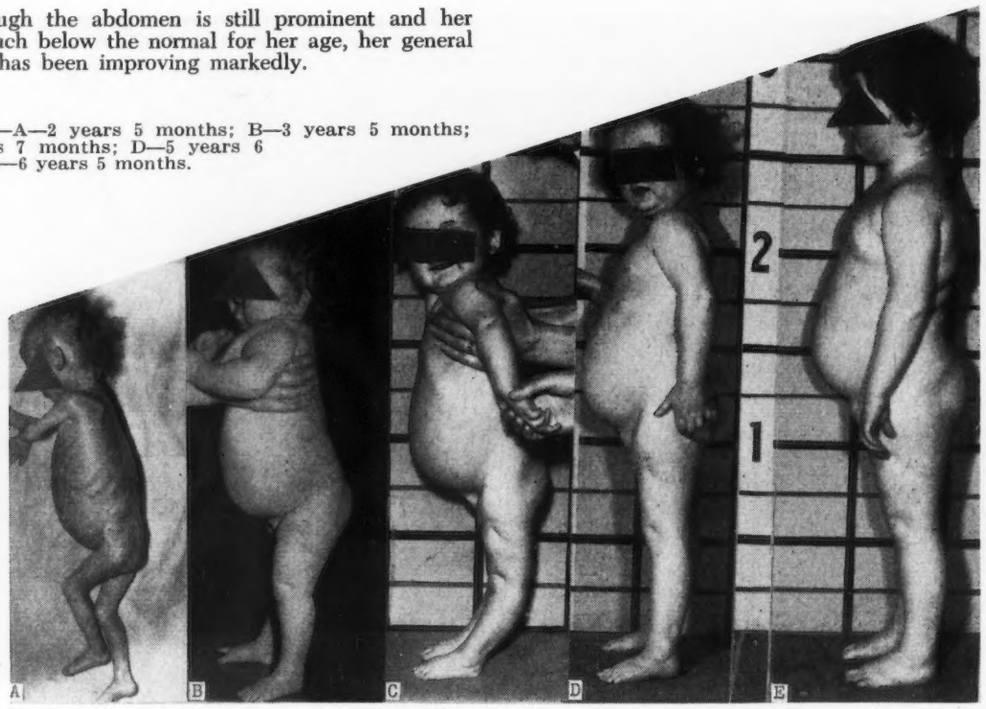

Fig. 6.—A—2 years 5 months; B—3 years 5 months; C—3 years 7 months; D—5 years 6 months; E—6 years 5 months.

SUMMARY

A review of the clinical picture of the cœliac syndrome is presented with indication of some of the factors which may contribute to the production of the disease. The importance of the role of infection and the type of infant feeding at the onset of the disease is stressed. Fat absorption studies indicate that a properly controlled patient should have reasonably normal fat absorption. The absorption of unsaturated fat is better than saturated fat.

There is a strong familial tendency in this disease, as shown by a study of the families of cœliac children and also in a study of twins.

The discovery that the gluten of cereal, particularly wheat, is deleterious in some cases has provided one of the greatest advances in the management of this condition.

The possible role of food allergy has been tested. While clinical trial would appear to support this as an etiological factor, skin tests with protein do not apppear to be of value.

Clinical experience with gluten-free diets, control of infection, the use of special starch recipes, and in severe and resistant cases the judicious use of cortisone, indicates that significant advances in our management of this disease have been made.

APPENDIX

Recipes which have been found useful as substitutes for bread, cake and cookies are as follows:

Gluten-free Wheat Starch Bread—

1-3/4 cup gluten-free wheat starch
1/3 cup sugar
3 tsp. baking powder
4 tbsp. margarine
2 egg whites
2/3 cup milk

Sift the dry ingredients together. Cut in the margarine. Add the egg whites and beat thoroughly. Add the milk and beat thoroughly. Pour batter into a small greased loaf pan. Bake at 400° F. for about one hour.

Note: This bread has a fine, close texture and may be toasted.

Crisp Cookies—

1 cup rice flour (or 1 cup soya flour)
1/2 tsp. baking *soda*
1/2 tsp. salt
Sift together, and set aside
Beat well
1/3-1/2 cup margarine
1/2 cup white sugar
1/4 cup brown sugar, well packed
Then add
1 unbeaten egg
1 tsp. vanilla

Add dry ingredients to this, mix well, then drop by teaspoon on ungreased cookie sheets about two inches apart, and flatten them slightly with a moistened broad knife. Bake at 375° F. for about 10 to 12 minutes.

Muffins

1/2 cup margarine
1/2 cup white sugar
Beat well together, and add
1 tsp. vanilla
1 unbeaten egg
Beat well, and add
1/2 cup soya flour
1/2 cup wheat starch
1/2 tsp. salt
1/2 cup rice flour } sifted together
2 tsp. baking powder }

Add dry ingredients alternating with 1/3 to 1/2 cup skim or protein milk. Bake in large-size paper baking cups at 375° F. for 20 minutes. (N.B. 1 cup of rice flour or 1 cup soya flour may be used but use no more than 1/2 cup wheat starch.)

Crisp Gluten-free Cookies (with banana flakes)—

1 cup margarine
1 cup white sugar
1 egg
1/2 tsp. vanilla
1/2 cup dried banana flakes
1/2 cup soya flour
1 cup gluten-free wheat starch
1/4 tsp. salt
1/4 tsp. baking soda
2 tsp. baking powder

Cream together the margarine, sugar, egg and vanilla. Sift together all the remaining dry ingredients except the banana flakes. Add dry ingredients and the banana flakes to the creamed mixture. Mix well. Form into small balls about the size of walnuts. Place on greased cookie sheet and flatten with a fork. Bake at 350° F. for five to eight minutes.

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RÉSUMÉ

La maladie cœliaque est un trouble chronique de la nutrition résultant de la mauvaise absorption des graisses et d'autres aliments. Les selles varient de la constipation à la diarrhée. Le volumineux abdomen donne à l'enfant une apparence clinique bien connue. Le cliché radiologique de l'intestin montre une segmentation de la colonne barytée probablement causée par une sécrétion excessive de mucus. La croissance peut être retardée à la longue. Les doigts hypocratiques apparaissent tôt dans les cas graves et disparaissent à la guérison. L'anémie complète ce tableau, qui peut se prolonger au delà de la puberté. La dentition est non seulement épargnée, mais souvent de meilleure qualité que la moyenne. Le début de cette affection dans la moitié des cas est soudain et correspond à une infection telle qu'une dysenterie ou une nasopharyngite. Dans l'autre moitié des cas, le début est insidieux. On ne peut trouver d'altération histo-pathologique spécifique. La courbe de tolérance au glucose est basse si le glucose est donné par la bouche, normale s'il est administré par voie intra-veineuse. Les selles contiennent un excédent de graisse causé surtout par une mauvaise absorption que l'on peut améliorer presque à la normale avec un traitement approprié. Il existe une forte tendance familiale dans cette maladie. Un des grands progrès dans le traitement de cette affection a été réalisé en Hollande, pendant le guerre, lorsqu'on s'est aperçu que le régime de famine, pauvre surtout en farines de blé et de seigle, auquel la population était soumise, profitait aux enfants atteints de maladie cœliaque. De nombreux auteurs ont repris ces observations et ont démontré que le gluten des céréales pourrait être néfaste dans certains cas. L'allergie alimentaire a été incriminée; cependant, même si l'expérience clinique semble apporter quelque confirmation à cette théorie, les épreuves de cutiréaction ont été décevantes.

L'expérience clinique avec des régimes sans gluten, le contrôle de l'infection, l'emploi de recettes spéciales de fécules, et dans les cas graves et rebelles, l'usage judicieux de la cortisone, indiquent que nous avons accompli un important progrès dans la lutte contre la maladie cœliaque. M.R.D.

SEROUS AND SEROSANGUINOUS DISCHARGE FROM THE MALE NIPPLE

At the Memorial Centre for Cancer and Allied Diseases analysis of a series of 30 cases of male breast lesions which discharged serous or bloody fluid from the nipple showed it to be an unusual sign, yet it was an indication of malignancy in more than half. Treves and his colleagues report (*A.M.A. Arch. Surg.*, 63: 319, 1956) that of 577 cases of benign tumours only 12 (2.1%) had nipple discharge but 18 (13.7%) of 131 carcinomas showed it. Serous or serosanguinous nipple discharge is usually a sign of papilloma which may be malignant. There are no certain clinical signs by which to distinguish the benign from the malignant lesion.

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PRESENT-DAY ASPECTS OF RESEARCH ON THE ETIOLOGY OF PULMONARY TUMOURS*

THE OSLER ORATION

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THE SUBJECT which I have chosen for this lecture is one which would have passionately interested Osler himself, for internists and experimental clinicians meet on the common ground of this work.

Pathological and clinical aspects.—Statistics from institutes of pathological anatomy in Germany—where autopsy records were carefully kept day by day—had started to show, by 1924, a numerical increase in cases of carcinoma of the lung. Ten years later, this tumour, which had formerly represented only 1% of all human cancer, was over 15%; instead of occupying fifth place it was now in second place, immediately after cancer of the stomach. The increase in incidence was soon confirmed by pathologists in other countries. Statistical enquiries were immediately organized. Those instituted in the United States, from 1937 on, established that the frequency of pulmonary cancer had more than doubled during the last ten years. The same findings were obtained in Great Britain, Denmark, Sweden, Switzerland, etc.† In Canada, the incidence has increased five-fold in the course of 20 years. There has been much discussion as to whether this disquieting increase is real or apparent. Some authors explain it mainly by the improvements in diagnosis of deep-seated cancer, and the prolongation of life-expectancy in the countries under consideration. Others have replied to this criticism by pointing out that this phenomenon has not applied to other cancers, whose site made them just as difficult to diagnose in the past. On the other hand, the increase is mainly confined to males, whereas it is absent, or at any rate much less, in females. In fact, parallel with this increase in incidence, certain statistics have shown that the sex incidence, formerly one female to three males, has now reached one to ten, or even one to 18. In view of the facts briefly mentioned above, what explanation can be found? Before trying to reply to this question, it is important to recall certain theories concerning the histology of malignant tumours derived from the essential elements of bronchopulmonary tissues. Four types can be distinguished, of which the first three are the commonest: (1) squamous epithelioma; (2) cylindro-cubic cell carcinoma; (3) carcinomata with undifferentiated cells; (4) a rare type whose origin and nature are still under dispute in recent reports of new cases. Some authors have termed this "adenomatosis", to indicate that the condition remains benign for a long time; others prefer the term "alveolar carcinoma", which is intended to indicate the origin of the neoplastic elements.

Glandular cell cancers and undifferentiated cancers do not, in fact, appear to have played any part in the increased incidence of lung tumours, an increase which is confined to squamous epitheliomata. Only the last named are involved in the problem under discussion today. As for the adenomata, they are worth noting only because they are particularly common in some laboratory animals.

To sum up, it is necessary to consider what new causative factors might play a part in epidermoid metaplasia of bronchial epithelium, giving origin to the cancers which are more and more commonly observed in the male. The most plausible factors may be classified under three headings: (1) increase in atmospheric pollution by certain dusts and products of combustion; (2) exposure at work to carcinogenic agents; (3) the abuse of tobacco, and in particular of cigarettes. We will limit ourselves to an enumeration of these points rather than a critical review.

I. INCREASE IN ATMOSPHERIC POLLUTION

The experimental demonstration of the carcinogenic action of coal tar, soot, mineral oil, and in general the products of combustion of all organic compounds (in which at above 450° C. there are formed polycyclic hydrocarbons, especially 3,4-benzpyrene, well known to be carcinogenic), tends to incriminate an increase in the substances in the air, in the form of dust or of gas. The following have been successively condemned: road-tarring (although the tars usually employed are obtained at temperatures of 235 to 342° C. only); exhaust fumes from internal combustion engines; smoke from

*Given at the Annual Meeting of the Canadian Medical Association, Quebec, June 13, 1956.
†Fascicule 3 of the ACTA (Unio internationalis contra cancrum), Vol. 9, 1953, contains a symposium held at Louvain in which there are excellent reports and a full bibliography.

factories and steam engines, as well as domestic sources. It is hard to imagine the enormous quantity of dust polluting the atmosphere of large industrial cities. It has been calculated, for example, that in the Ruhr there is a deposit of on the average 1 to 3 kilograms per 100 square metres per month. In atmospheric dust and the exhaust gases of automobiles 3,4-benzpyrene has been discovered. The amount inspired with the air of a large industrial city by a human being in one year corresponds to 200 micrograms of this carcinogenic hydrocarbon.

This factor of air pollution would explain why lung cancer is commoner in city dwellers than rural inhabitants. On the other hand, it does not explain why it affects only males. It is true that differences in the sex incidence of certain cancers are known. As regards lung cancers, adenocarcinomata are known to be commoner in women; there may be a male predisposition to squamous epithelioma, whose incidence might be increased by adjuvant factors.

II. Occupational Exposure to Carcinogens

This factor is less hypothetical than the preceding. An abnormal incidence of lung cancer of squamous type has been reported among workers exposed to gases or dust which might reasonably be considered as the cause of the disease. As regards this etiology, the preference for males is explicable since they represent by far the largest group of workers. The causative agent might then be either physical or chemical.

(a) *Physical agents* with a possible carcinogenic action are all ionizing radiations. The first endemic focus of occupational lung cancer was recognized many years ago, in 1879, among the miners of the Erzgebirge, whose ore is well known to be rich in uranium. Since 1922, investigations have been made and a relationship has been established between the radon concentration and the concentration of radioactive dust in mine shafts, and the incidence of cancer in underground workers. The present-day expansion of prospecting and the working of new uranium mines might then (if preventive measures are not taken) lead to an increase in lung cancer after a delay of at least a decade.

However, all radiations are carcinogenic. It is reasonable to wonder whether the growing practice of radiological examination of the lung (commoner in men than in women) is completely unrelated to the problem under discussion.

(b) Among *chemical substances,* those enumerated in the above paragraph as atmospheric pollutants are common in certain occupations. However, opinions differ among authors who have tried to establish statistically a particular occupational predisposition to lung tumours.

This is also true of various mineral dusts, notably those of chrome, asbestos and arsenic. In certain countries, where there are workings containing these substances, a high incidence of lung cancer has been observed among the miners; this high incidence has not, however, been found in mine workers in other countries. In any case, the tumours have been found to be endemic in factories where arsenic or chromates are prepared.

This is also true of places of manufacture of asbestos (which has greatly increased in use in the last few decades); the condition is encountered in both women and in men employed in this way. The incidence of lung cancer is said to be as high as 12 and even 20% among subjects suffering from asbestosis.

To sum up, a striking multiplicity and variety of agents are already known as possible factors in the origin of lung cancer. This accounts for the difficulty in tracing their long-term effect in case histories.

III. Abuse of Tobacco, in Particular Cigarettes

It has long been suspected that tobacco plays a part in the production of tumours. But the term "smokers' cancer" has changed its anatomical site since I was a student. At that time it referred to epithelioma of the lip, considered to be particularly common in pipe smokers; it is now bronchial epithelioma in cigarette smokers.

There are no available statistics indicating a diminution in lip tumours now that cigarette smoking is fashionable, but studies have been undertaken during the last 15 years on the smoking habits of patients suffering from lung cancer. Studies of this nature, partly carried out in Germany, Great Britain and the United States, have not always given similar results. Nevertheless, most authors (especially those whose studies are recent and detailed) bring out two arguments in favour of a causative relation: (1)

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The parallelism between the total amount of tobacco smoked in a country and the increase in the incidence of lung cancer. In reality this type of argument might just as well be applied to almost all the agents mentioned above. (2) Ideas resulting from questionnaires among patients hospitalized for lung cancer and a similar control series of persons of the same age, sex and social status, under treatment in the same hospitals for other conditions. The proportion of smokers is markedly greater in the former group; the percentage of cancers increases especially with the number of cigarettes smoked, much more than in the case of cigars or the pipe. Pulmonary tumours are observed 10 or even 20 times more commonly in heavy cigarette smokers than in non-smokers.

For a long time it has been suspected that carcinogenic hydrocarbons are formed during combustion of the cellulose in tobacco. The temperature of combustion varies, according to whether the tobacco is in cigarette form (600 to 740° C. according to the rhythm with which the smoker inhales and the consistency of the cigarette), or of a cigar or pipe which undergoes combustion at much lower temperatures. Recently, 3,4-benzpyrene has been detected and even estimated in tobacco smoke. Production has been estimated at about 100,000,000th of a gram per cigarette. In that case the smoke produced from 40 cigarettes a day, for one year, would represent only three-quarters of the quantity of benzpyrene inhaled during the same period in the dust of large cities. It is true that tobacco tar is a peculiarly complex mixture, containing a very large number of substances; more than 25 polycyclic hydrocarbons have already been isolated from it. It is probable that 3,4-benzpyrene is not the only carcinogen present.

All that has just been said shows that the problem of the etiology of bronchopulmonary cancer is very far from being solved. Hence, many workers have tried to solve it experimentally.

IV. EXPERIMENTAL ASPECTS

For more than 25 years attempts have been made to produce bronchopulmonary cancer in laboratory animals.

The first attempts were by inhalation of gas, vapour, smoke and dust, the animals being kept in a closed vessel whose atmosphere was polluted with these substances. The substances have also been introduced by intratracheal injection, and more recently as aerosols. In addition, it has been shown that the application of tar to the skin of mice may cause tumours to appear in their lungs. Lastly, the test substances have been introduced by subcutaneous or intravenous injection.

It is impossible to review all the numerous publications on this subject, often reporting contradictory results. We will limit ourselves to a discussion of each of the three experiments enumerated above: inhalation, painting, injection.

1. *Studies of direct introduction of substances into the respiratory tract.*—Animals have been made to breathe combat gases, aniline and its derivatives, various mineral dusts, suspension or vapour of coal tar, sweepings from tarred roads, exhaust gas from automobiles, cigarette smoke, etc. Tumours were never produced in rabbits or rats, in which spontaneous lung cancer is rare. In a few cases, a proliferative reaction of the bronchial epithelium has been reported but has never gone on to malignancy. Malignant tumours obtained were almost all sarcomata, produced by intratracheal injection of 3,4-benzpyrene or of methylcholanthrene.

On the other hand, several experiments with mice have made it clear that the agents utilized were responsible, in more or less high proportions of cases, for pulmonary tumours. However, these results should be interpreted with great reserve, for they are always examples of adenomatosis, which we mentioned previously. This tumour, very rare in man, is on the contrary common in the mouse where it appears spontaneously, sometimes in a high proportion in certain selected strains. Moreover, it is easily and abundantly produced by repeated administration of both physical agents (such as exposure to x-rays) and chemical agents.

We cannot fail to be surprised by the equivocal results of inhalations. A high incidence of adenomata has indeed been reported in mice which for months inhaled the dust from tarred roads. But with cigarette smoke, results published by different authors are entirely contradictory. Some have reported a percentage of pulmonary adenomata two or three times greater than in controls. On the other hand, a great number of other authors have never observed an

increase in the incidence of tumours, even in animals exposed to such atmospheres for the whole of their lifetime. These results are perhaps due to genetic differences in the strains of mice used. It is also advisable to relate these experimental failures to the finding that, in man, the adenomatous type does not appear to be commoner in smokers.

2. *Transcutaneous induction.*—This procedure is much more effective and constant than the preceding one. The high incidence of pulmonary adenomata in mice painted with coal tar was established over 30 years ago. Also, this method of production has been repeatedly used for study of these tumours, since carcinogenic hydrocarbons give similar results. It is advisable to distribute the painting between various skin areas in order to prevent the early-developing skin cancers from killing the animal before the later pulmonary tumours appear. It is also possible to induce pulmonary adenomatosis by applications to the mucous membranes (rectum, vagina, stomach).

However, in this case also, it does not appear that the many research workers trying to induce skin cancer by application of cigarette tars have reported the appearance of pulmonary tumours in their animals. Furthermore, the great majority of them have not even succeeded in obtaining skin epitheliomata. This negative result may be explained by the very small quantity of carcinogen contained in the product of combustion utilized. It is advisable to use a very concentrated tar obtained from a large number of cigarettes and freshly prepared. By this means skin cancer may be produced, but in a variable proportion depending on the strain of the mouse.

3. *Injection.*—This is the procedure by which lung tumours are most readily produced. Substances capable of inducing them in mice are numerous among the polycyclic hydrocarbons and their nitrogen analogues, whether administered subcutaneously, intravenously or intraperitoneally. Urethane, a water-soluble substance, is particularly active in this way and has been used for studies of histogenesis of this tumour type.

Production of sarcoma at the site of injection of cigarette tar has been reported, but the simultaneous appearance of lung tumours has not been mentioned.

SUMMARY AND CONCLUSION

This rapid review of clinical, pathological and experimental facts concerning the etiology of pulmonary tumours demonstrates the uncertainty prevailing today in spite of many publications on this problem.

The general title "bronchopulmonary cancer" really includes several types of tumour, differing histologically in their development, and no doubt also etiologically. Attention has been particularly focused for several decades on one of these neoplasms, squamous epithelioma of the bronchi. Attempts have been made to determine the reason for its increasing incidence in males and to verify the more important among the suspected factors. Unfortunately, this investigation does not lend itself well to experimental study. Among laboratory animals, pulmonary tumours are easily induced only in the mouse, and even then they are not squamous epitheliomata. Nevertheless, the considerable amount of work done with mice has shown that the atmospheric introduction of carcinogens is not the best method.

Without seeking to diminish the importance of results obtained in investigations of patients with pulmonary cancer, it is permissible to speculate whether these have not undergone a rather one-sided orientation.

Carcinogenesis in the lung is probably the result of repeated insults by various agents, such as have already been recognized in the etiology of some other malignant tumours. These insults have cumulative effects over the years on a single and genetically susceptible cell-type.

Apart from the known carcinogens, it is probable that others, introduced into the body by the digestive tract or transcutaneously (quite apart from what an individual may receive by injection), take part in the process of development of lung cancer.

INVESTIGATIONS ON PATHOGENESIS OF SO-CALLED FAT EMBOLISM

Johnson and Svanborg from Stockholm (*Ann. Surg.*, 144: 145, 1956) report experimental work on rabbits to refute the concept that fat emboli consist of marrow fat torn loose through injury. The frequency of fat embolism is not proportionate to the quantity of lipids in the serum. It cannot be considered definitely established that the occurrence in the organ capillaries of fat colorable with sudan is of any clinical importance.

THE ROLE OF IRRADIATION IN THE TREATMENT OF CARCINOMA OF THE CORPUS UTERI*

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CARCINOMA OF THE corpus uteri has been the subject of numerous medical treatises within the last few years. The many common factors seen in patients with this disease have intrigued investigators searching for the "cause of cancer"; heredity, endocrines, and biochemistry all seem to play a part in the etiology.

Radiologists are clinicians as well as therapists, and when a patient with cancer of the corpus uteri presents herself for treatment we cannot help but be interested in the many common characteristics which these women display, and speculate on their relationship to the cause of cancer. These characteristics are so usual that a cancer type has come to be recognized. Fig. 1 is a prototype of this woman. McGarvey[1] describes her as follows:

> "Adenocarcinoma of the endometrium is most frequently encountered in the sterile or infertile woman, between the ages of 56 and 60 years, who has had a slightly delayed menopause. The climacteric was commonly complicated by periods of menorrhagia. Hypertension, obesity, and diabetes mellitus were other disorders which were often associated with the development of the neoplasm. The whole picture is suggestive of a common metabolic disorder created by endocrine dysfunction. The abnormal metabolism provides the extrachromosomal factor essential to the development of carcinoma in the individual predisposed by heredity."

Way[2] believes that overactivity of the anterior pituitary is the common factor in all these disorders and the one to be inherited. Further light on this absorbing problem of etiology will be shed as large series of cases of cancer of the corpus are studied and reported. Here the radiologist has the opportunity of being part of a team in clinical investigation. In our series of 149 cases, 73% had one or more of the characteristics associated with this type; obesity, delayed menopause and hypertension were commonly found in the same patient.

The treatment of cancer in this site has been a bone of contention among surgeons, gynæcologists and radiologists, and it is with the thought that we can progress only by careful analysis of our methods of treatment and results that we present this paper.

For many years cancer of the uterus, cervix as well as corpus, was considered to be a purely surgical problem. But the results of treatment were so poor, especially in cancer of the cervix, with not more than a 10% survival rate, that European gynæcologists, notably those of France and Sweden, turned to radium and x-rays for treatment early in the century, a very few years after their discovery.

Heyman[3] was one of the first to use radium for cancer of the corpus. At first he treated only patients who were considered to be incurable; these did so well that he was encouraged to use it for early cases as well, often following the radium treatment by hysterectomy. Surprisingly, often the pathologists could find no residual carcinoma in the uterus. Because of this Heyman began to reserve hysterectomy for cases of failure, that is, for those cases in which the cancer was not controlled by radium, or recurred. Originally he used the tandem container but he soon learned that this inflexible instrument could not give the desirable uniform dose of irradiation to the large uterus with irregular cavity, so often found in cancer of the uterine body. For this reason Heyman developed a system of packing the uterus with multiple radium sources, and experience proved this to be a better method of treatment. On the basis of clinical trial and actual measurement he and his physicist Benner[4] found that an adequate and homogeneous dose was obtained when 10 irradiators completely filled the uterine cavity and were left in that position long enough to produce 1,500 milligram-hours. This empirical plan of treatment was found to deliver a minimum dose of 1075 r on the serosal surface of the uterus. Accepting this as the minimal requirement, tables were compiled to show the time necessary to give this dose for any given number and size of irradiators required to completely fill the uterus.

Batho of the British Columbia Cancer Institute has modified Benner's table of experimental results for our 10 milligram radium sources and has added an estimate of the maximum dose on the endometrial surface (Table I).

*Presented to the Section of Radiology at the Conjoint B.M.A., C.M.A., O.M.A. Annual Meeting, Toronto, June 1955.

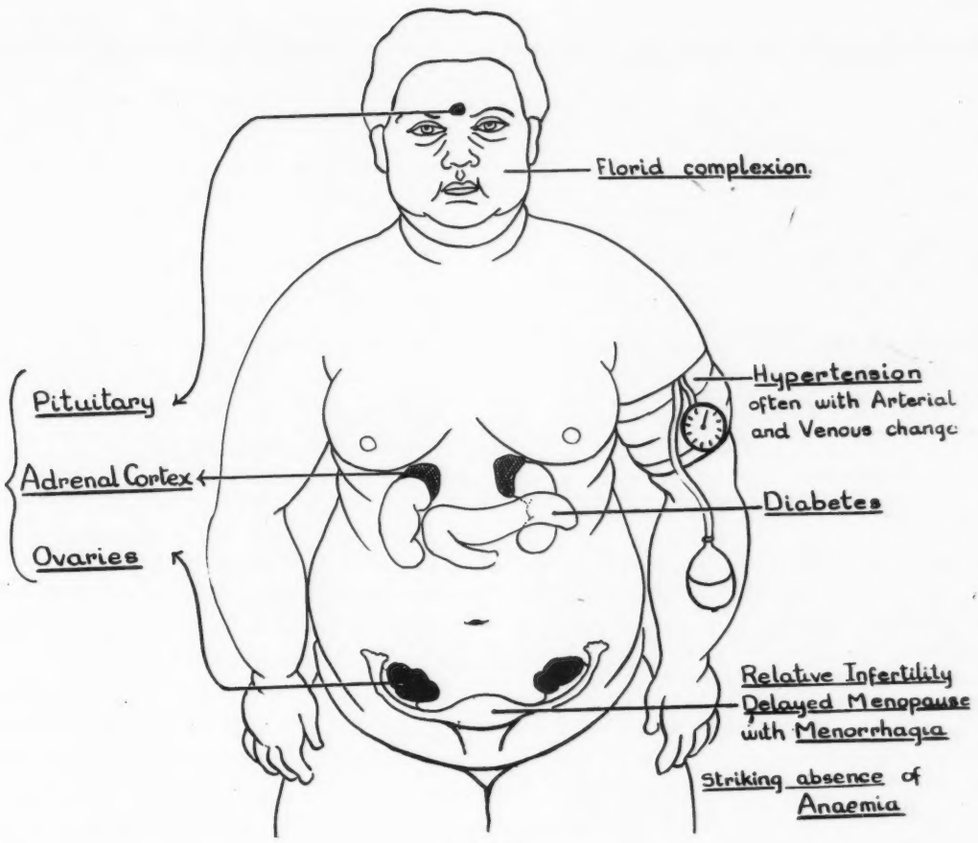


Fig. 1

We attempt to deliver 1750 r as calculated for the serosal surface on each of two occasions, approximately three weeks apart. This has been estimated at 1.5 cm. from the endometrium. Benner's estimation was on the basis of 1 cm., hence the difference in dosage. Photographs of the instruments used and of typical applications have appeared frequently in the literature.

The technique of packing is simple. The size of the cavity is estimated after dilatation of the cervix, and the size of irradiators chosen. The attached wires with their numbered labels protrude through the introitus. In all but very early cases deep x-ray therapy precedes or follows radium treatment. Since the advent of supervoltages and Cobalt 60, the obese woman is no longer a problem, for it is now a relatively simple matter to deliver an adequate tumour dose to the pelvis. This is of vital importance when the disease has either spread beyond the uterus or has been reported as anaplastic, and is in fact inoperable.

Heyman's results following the adoption of the packing technique rivalled those from sur-

TABLE I.

TREATMENT TIMES AND NUMBER OF MILLIGRAM-HOURS FOR A CONSTANT MINIMUM DOSE OF 1750 r* WITH DIFFERENT NUMBERS OF APPLICATORS OF DIFFERENT SIZES

	Size of applicator					
	Small			*Medium*		
No. of applicators	*Hours*	*MG. - HR.*	*Approximate maximum†*	*Hours*	*MG. - HR.*	*Approximate maximum†*
4	36.5	1,460	20,800 r	——	——	——
7	28.9	2,025	15,100	31.9	2,230	12,500 r
10	24.4	2,440	12,800	26.1	2,610	10,700
13	21.2	2,750	11,500	22.8	2,960	9,400
16	19.2	3,075	10,600	20.2	3,235	8,900

*On the serosal surface of the uterine wall—assumed to be 1.5 cm. thick.
†The approximate maximum exposure on the endometrial surface.

TABLE II.

CARCINOMA OF CORPUS UTERI
149 CASES SEEN WITH VIEW TO TREATMENT (1938 - 49 INCLUSIVE)

A. Cases given primary treatment	*Total number cases*	*Number cases*	*Number surviving 5 - 15 years*	*%*
(1) Intracavitary radium		98	52	53.1
(2) Incomplete radiation (palliative)		11	0	
(3) No treatment		2	0	
Total	111			46.8
B. Cases treated elsewhere and referred				
(1) For P.O. radiation		19	12	
(2) For treatment vaginal recurrence		12	4	
(3) For treatment recurrence elsewhere		7	0	
Total	38			42.1
Totals	149	149	68	45.6

gery, with the result that some American gynæcologists, notably Arneson[6] and Scheffey,[7] began to use intracavitary radium as a preliminary to surgery. What is known as the "planned technique" – that is, multiple-source intracavitary radium followed by hysterectomy and bilateral salpingo - oophorectomy – came into vogue. Scheffey has this to say: "Irradiation tends to promote local devitalization and attenuation if not complete destruction of the growth, reduction of infection and sealing of lymphatics, thus lessening the possibility of cancerous dissemination when surgery is employed later on, and finally, reduction of the incidence of recurrent growth in the vaginal vault scar." He reports a 5 to 15 year survival rate of 91.3% for a small group of cases treated by this planned technique. These are of course early and carefully selected cases, but this is a high survival rate by any standard and merits attention.

Cosbie[8] is also in favour of this planned technique, as he intimates in his analysis of the 421 patients observed at the Toronto General Hospital between 1937 and 1952. This was the same sort of heterogeneous group of patients admitted to most large gynæcological clinics of general hospitals, and Cosbie has analyzed it from various points of view. For the 234 admitted between 1937 and 1947 there was an over-all 5-year survival rate of 46.2%; for 68 surgically treated cases it was 63.2%, and for 47 treated by the planned technique it was 70.2%. On the other hand many gynæcologists, both in England and on this continent, believe that immediate operation is the treatment of choice, and should be done in all operable cases.

Heyman early recognized the fact that the value of different methods of treatment can be estimated only by comparing results of uniform and clinically comparable groups of patients. Under his editorship a subcommittee on the registration of cancer of the World Health Organization[9] set up a classification by stage of disease for cancer of the corpus. This was adopted in 1950 and complements the study of cancer of the cervix initiated in 1928 by the League of Nations.[10] A more simple stage grouping has been used for the corpus:

Stage 0.—*Cases which show a suspicion of malignancy,* i.e., those which the pathologist considers most likely to be of a carcinomatous nature though it is impossible to arrive at a definite microscopic diagnosis.

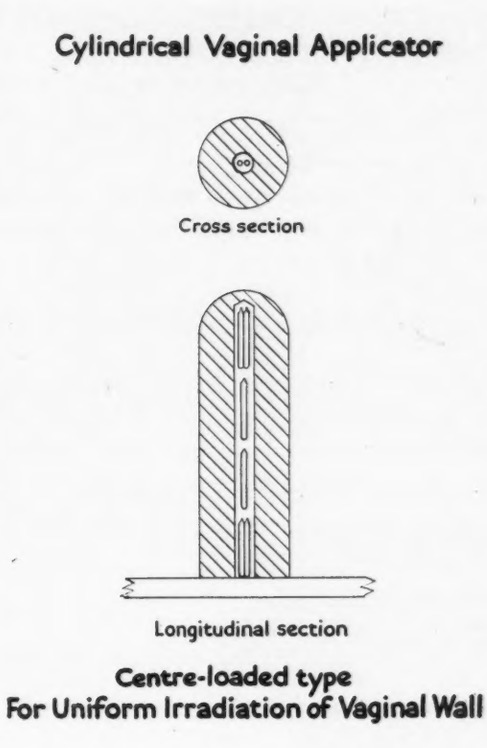
Stage I.—*The growth is confined to the uterus.* Group 1: operation advisable. Group 2: bad operation risk.

Stage II.—*The growth has spread outside the uterus.*

Since the introduction of this new stage grouping more institutions are reporting their results on a comparable basis, and further experience should reveal whether one method is superior to the other. Heyman[11] believes that in the meantime each leading institution should maintain and develop the treatment method it considers the best and defer decision on this controversial matter until it can be based on statistically significant figures.

REVIEW OF B.C. SERIES

Our review covers patients treated at the British Columbia Cancer Institute and privately



(Courtesy of R. H. Moffat, M.D.)

Fig. 2

between 1938 and 1949 and is comprised of 149 patients examined with a view to treatment. An analysis of this heterogeneous group in terms of methods of treatment and survival is shown in Table II.

Influenced by Heyman's method of reporting, we have made two main groups: A. Those referred for primary treatment (111). B. Those who had had primary treatment elsewhere (38). Group B would be excluded from the World Health Organization International Reports.

One hundred and eleven of our patients fall into group A. In this group, where possible, treatment was by intracavitary radium, and this was followed by surgery or by x-ray therapy. Ninety-eight were treated in this manner and for these there is a 5 to 15 year relative survival rate of 53.1%. In this connection it is noteworthy that of the 46 in the group who did not survive for 5 years, 9 died of other causes and were free from cancer. The 13 referred for palliation died within a short time of admission. In 2 cases the condition was too advanced for treatment; the others had small doses of irradiation, mostly because of hæmorrhage.

Thirty-eight were in group B. Of these 19 were referred for postoperative irradiation, and 19 for the treatment of recurrent disease which in 12 cases was in the vagina. Of this group of 38, 16 lived for 5 to 15 years, including 4 of those treated for vaginal recurrences.

Recurrences in the vagina are not uncommon, and in an attempt to prevent these additional radium is placed in the vagina. We believe that this should also be a routine postoperative procedure. The vagina is the most common site for metastatic disease and reports suggest that a certain proportion can be prevented by this supplementary treatment. For example, Dobbie[12] reports 11% vaginal recurrences after hysterectomy alone, 2.4% when radium treatment followed hysterectomy. Vaginal recurrences after either surgery or irradiation may be treated by some type of local radium, and various types of applicators have been devised. A cylindrical one in use at the British Columbia Cancer Institute is shown (Fig. 2).

The patient wears the applicator for several hours a day until the desired dose has been delivered. This has proved to be about 6000 r over a period of 7 to 8 days measured on the rectovaginal septum.

Since the latter part of 1949 and with the cooperation of gynæcologists we have been able

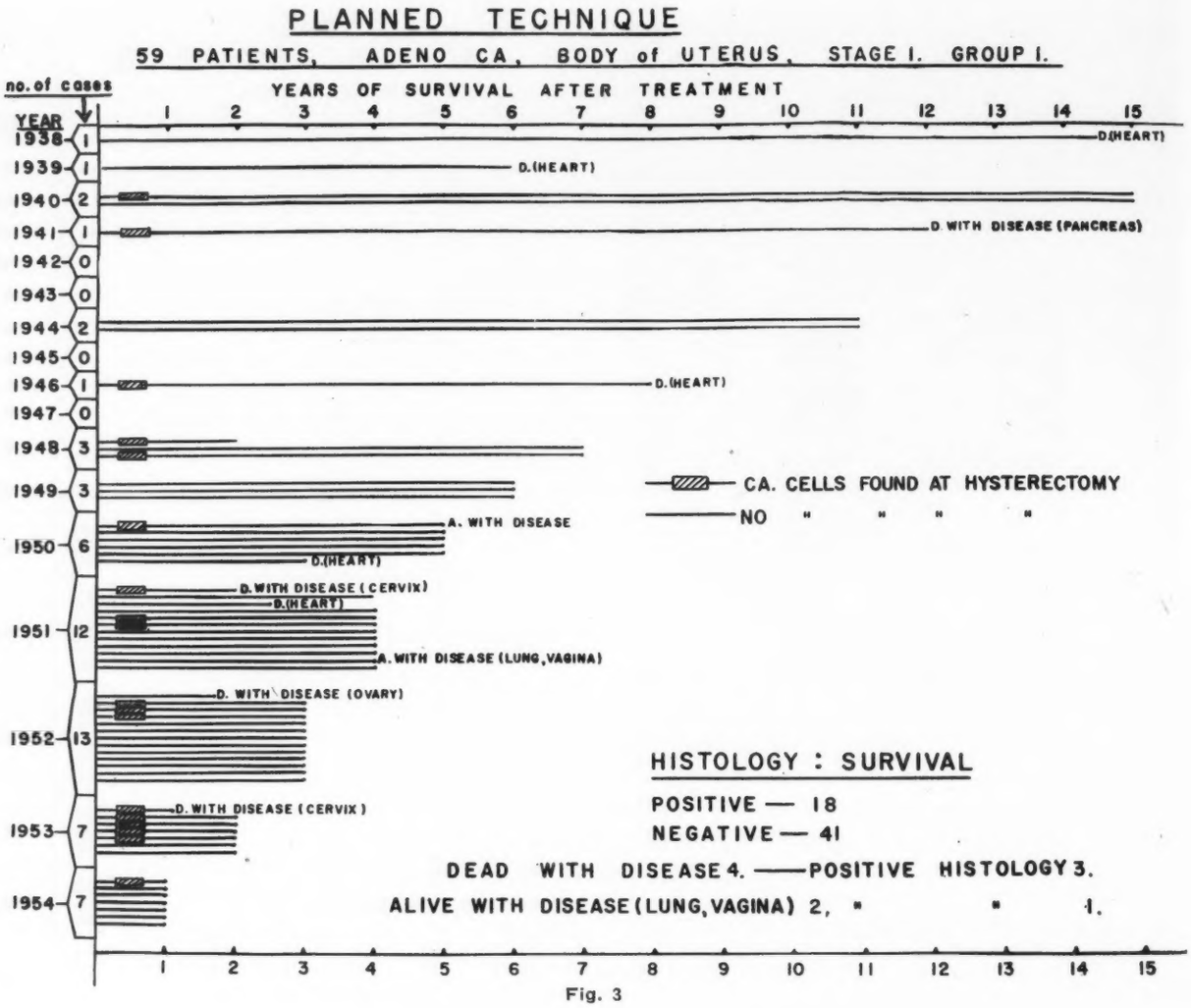


Fig. 3

to embark on the "planned technique" for a greater number of patients. Between 1938 and 1954, 59 were so treated. This is shown in Fig. 3 and Table III.

TABLE III.

59 CASES TREATED BY PLANNED TECHNIQUE FROM 1938 - 1954 (INCLUSIVE)

	Residual disease in uterus	*No disease in uterus*
Alive and well	12	36
Alive with disease	1	1
Dead with disease	3	1
Dead without disease	2	3
Totals	18	41

Each line represents the life-line of an individual patient. A hatched bar indicates residual disease in the uterus at the time of hysterectomy. This is seen in 18 cases.

Of these 18 patients, 12 are alive and well, 1 is alive with disease, and 3 have died with disease; it is worth noting that 2 of these cases had squamous-cell carcinoma of the cervix as well, and were not really operable. Two have died without carcinoma, one after 8 years and one after 6.

It will be seen that this method of treatment has been extended to a greater number of patients in recent years. This increase began in 1949 when pre-treatment consultations between gynæcologists and radiotherapists became a routine procedure.

The presence or absence of residual disease in the uterus is often difficult to determine because of the profound effect of radiation upon the cells. This is shown in the sections (Figs. 4 and 5) from the same uterus (courtesy of Dr. I. D. Maxwell).

The first (Fig. 4) is of the tissue originally diagnosed as adenocarcinoma of the corpus. The

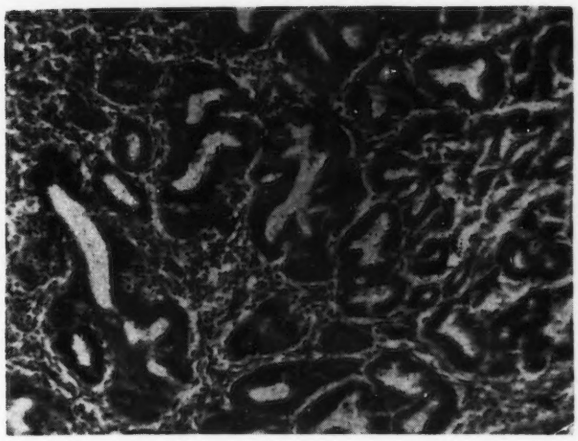


Fig. 4

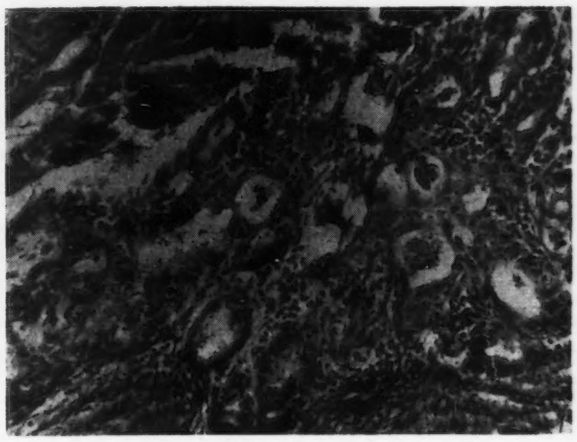


Fig. 5

second (Fig. 5) is of tissue from the same uterus 8 weeks later, and after irradiation. It will be seen that the cells on this second slide are large, pale and vacuolated—typical radiation effects; originally they could have been either cancer cells or normal cells. Of more importance is the glandular structure. The glands are bunched up and malformed, and pathologists tell us they could not in any way be mistaken for normal glands. There was residual carcinoma in this uterus.

DISCUSSION

In summary, it seems fair to say that irradiation has a useful place in the treatment of all stages of carcinoma of the body of the uterus.

Stage 0. For poor surgical risks.

Stage I. (a) Treatment of choice as advocated by Heyman, i.e. by means of multiple-source intracavitary radium. (b) Preoperative—"planned technique". (c) Postoperative—more advanced cases. (d) Poor surgical risks and anaplastic disease. (e) Prophylactic treatment—to prevent vaginal metastases.

Stage II. (a) Full radiation treatment with a hope of cure. (b) Palliation, including distant metastases.

We believe the "planned technique" to be a definite improvement in the treatment of operable cases. It will be some years, however, before any valid comparisons can be made. Meanwhile co-operation between gynæcologists and radiotherapists is of vital importance; perhaps this is the most important consideration of all, because this sort of team work presupposes well-trained surgeons and radiotherapists, adequate and comparable records, and complete follow-up of patients.

With respect to irradiation, the next important advance will doubtless be in the field of radiobiology. As a result of nuclear research, physicists have given us already far more than we need in the way of actual power—supervoltages hardly dreamed of a few years ago. Biologists must now help us to a better understanding of the ionizing effects of radiation in living tissues. Research centres in many parts of the world are engaged in this vital problem. Edith Paterson and her co-workers at the Christie Cancer Hospital and Holt Radium Institute in Manchester have been working on it for many years. These efforts on the part of radiobiologists should eventually enable radiotherapists to use their phenomenal instruments in a more exact and less destructive manner.

It is evident that both surgery and irradiation have a very important part to play in the treatment of carcinoma of the corpus uteri, either alone or in combination. Advanced cases fall automatically to the radiotherapist. It is his responsibility to ensure that the patient herself is not forgotten in the current preoccupation with supervoltages, isodose curves, and rotation techniques or dwarfed by the vistas of physical and technical accuracy which these have opened up. Their use has greatly simplified the ordeal of treatment for both the patient and the radiotherapist, but only time and experience will show the effect they have had in terms of morbidity and survival. In the meantime a great deal may be learned by reviewing the subject in the light of the wisdom propounded by the pioneers in radiotherapy, the ones who first used radium in the treatment of cancer of the uterus, Regaud of Paris, Heyman of Stockholm, Kelly of Baltimore, Elizabeth Hurdon of London. Their pre-

cept and example of the careful clinical evaluation of each patient in relation to her disease and its treatment remain the foundation of successful radiotherapy. "There is no substitute for experience and judgment cannot be imparted by the pen."[13]

We wish to express our appreciation to Dr. H. K. Fidler, Dr. H. H. Pitts and Dr. I. D. Maxwell for their pathological work incident to this presentation, to Dr. A. M. Agnew and his gynæcological staff, and to the Records and Photographic Departments of the British Columbia Cancer Institute.

RÉSUMÉ

Les auteurs croient juste d'affirmer que l'irradiation est utile dans le traitement du carcinome du corps de l'utérus à tous le stages, et que la technique d'irradiation préopératoire organisée en vue de l'intervention représente une réelle amélioration dans le traitement des cas opérables. Toutefois, il s'écoulera plusieurs années avant qu'on puisse établir des comparaisons valables. La coopération entre les gynécologues et les radiologistes est d'une importance vitale; elle est même le point le plus important de cette technique, parce que ce travail d'équipe présuppose des chirurgiens et des radiothérapeutes expérimentés, un système de fiches suffisant pour faire des comparaisons, et des observations sur chaque malade pendant plusieurs années.

A propos d'irradiation, la prochaine étape de progrès sera sans doute dans le domaine de la radiobiologie. Comme résultat des recherches nucléaires, les physiciens ont déjà mis à notre disposition plus d'énergie que nous n'en pouvons utiliser—des supervoltages qu'on soupçonnait à peine il y a quelques années. Les biologistes doivent maintenant nous aider à mieux comprendre les effets d'ionisation de la radiation dans les tissus vivants. Dans les centres de recherches de plusieurs pays, on s'acharne à éclaircir ce problème vital. Edith Paterson et ses collaborateurs du Christie Cancer Hospital et le Holt Radium Institute de Manchester y travaillent depuis plusieurs années. Ces efforts de la part des radiobiologistes devraient éventuellement permettre aux radiothérapeutes de se servir de leurs moyens extraordinaires d'une manière plus exacte et moins destructrice.

Il est évident que la chirurgie et l'irradiation ont à jouer un rôle très important, soit seules, soit combinées, dans le traitement du carcinome du corps de l'utérus. Les cas avancés reviennent automatiquement au radiothérapeute; c'est à lui qu'incombe la responsabilité de s'assurer que la patiente elle-même n'est pas oubliée parmi les calculs de supervoltages, des courbes d'isodose et de techniques d'irradiations rotatoires, ou qu'elle ne disparaît pas derrière les perspectives d'exactitude physique et technique qui en résultent. L'emploi de ces savants moyens a grandement diminué la rude épreuve du traitement, et pour la patiente et pour le médecin, mais ce n'est qu'avec le temps et l'expérience que nous pourrons en juger au point de vue morbidité et survie. En attendant, il peut être très profitable de revoir, sur ce sujet, les sages opinions des pionniers de la radiothérapie, ceux qui se servirent les premiers du radium pour traiter le cancer de l'utérus: Regaud, de Paris; Heyman, de Stockholm; Kelly, de Baltimore; Elizabeth Hurdon, de Londres. Leur précepte et leur exemple d'évaluation clinique judicieuse de chaque patiente relativement à la maladie et à son traitement demeure la base d'une heureuse radiothérapie, à savoir: "Il n'y a pas de substitut pour l'expérience, et le jugement ne s'acquiert pas dans les livres." M.R.D.

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AN EVALUATION OF THE ACCURACY OF DIAGNOSIS IN PLACENTA PRÆVIA*

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WITH CONSERVATIVE TREATMENT the fetal loss in placenta prævia should be reduced. Davis[1] in a review of 325 cases of placenta prævia with immediate intervention reported a fetal mortality of 32%, and Browne[2] in 3,103 cases with similar management reported a fetal death rate of 53%.

*From the Department of Obstetrics and Gynæcology and the Department of Radiology of the Toronto General Hospital.

The results obtained with expectant treatment by Johnson[3] and by Macafee[4] were sufficiently encouraging to establish this form of management generally under suitable circumstances. Johnson[3, 5] in 1945 in 79 cases showed a fetal loss of 22.2% and in 1950 in 201 a loss of 21%. Macafee[4] in 174 cases in 1945 showed a comparable figure of 23.5% fetal mortality. Since then, Schmitz[6] has recorded a fetal loss of 23% in 112 cases, Bender[7] 16.8% in 113 cases and Williams[8] 12% in 105 cases which he was able to manage conservatively. It would appear that a loss of 30% of infants in placenta prævia prior to expectant management was reasonable, and since then a loss of 20% might be considered a good result.

Experience on the public service of the Toronto General Hospital was not so encouraging. In 191 cases of placenta prævia from 1928 to 1944, the fetal loss was 29%. From 1945 to 1952, however, in 57 cases the loss in viable infants was 38.6%. Maternal mortality had fortunately fallen from 2.6% to 0. In the hope of improving this loss of infants a routine of management was introduced in 1953:

1. Patients with vaginal bleeding in the third trimester of pregnancy are admitted to hospital.

2. Blood is cross-matched and kept readily available.

3. In those cases where placenta prævia is suspected or cannot be excluded, the placenta is localized radiologically when bleeding has stopped.

4. A vaginal examination is performed on all cases in the delivery room, which is arranged for Cæsarean section if necessary. This examination includes speculum visualization of the cervix and vagina and palpation of the fornices.

5. In cases of placenta prævia near term or continuing to hæmorrhage, pregnancy is terminated in the manner appropriate to the particular case.

6. When placenta prævia is diagnosed before the 37th week, the patient is kept in hospital under observation until fetal maturity gives a reasonable chance of survival of the child or hæmorrhage recurs.

7. Patients with a minor cause of bleeding are discharged when the previously outlined investigation is completed, usually in about two days.

The social upset and the expense of prolonged hospitalization requires a reasonably certain diagnosis of placenta prævia when conservative treatment is undertaken. Localization of the placenta by x-ray has been attempted by numerous methods. Stevenson[9] using soft tissue technique in 474 cases in which the placenta was visualized reported a correct diagnosis in 98.1%. Johnson[3] feels that while placental visualization is valuable if the films can be interpreted by a radiologist skilled in soft tissue work, there are too few of these experts available. The difficulty experienced at the Toronto General Hospital was in obtaining consistently good soft tissue films when numerous technicians were responsible for them. Consequently, since 1953 a modification of Reid's[10] method of placental localization has been used. This gravitational method depends upon the fact that the specific gravity of the fetus is such that it sinks through liquor amnii, and therefore displacement from certain known anatomical points can only be due to the placenta or some other abnormal structure. These known points are: (1) the symphysis pubis; (2) the sacral promontory; (3) the walls of the pelvic inlet; (4) the internal os of the uterus; (5) the junction of the upper and lower uterine segments.

On a lateral film of the pelvis, before labour, the internal os is at the level of the ischial spines, and the junction of the upper and lower segments of the uterus is at the pelvic brim. With a 36-inch (90 cm.) tube-film distance the uterine wall appears as a shadow 1 to 1.5 cm. thick and the placenta and uterine wall together as a shadow 4 to 7 cm. thick. The diameter of the average placenta at this tube-film distance is 22 to 25 cm.

RADIOGRAPHIC TECHNIQUE

The gravitational method of placental localization is carried out as follows:

1. The patient's bladder is emptied by catheterization just before radiological examination.

2. Using a 36-inch tube-film distance, films are taken as follows:

(i) With the patient lying supine on the table, the table tilted at 45° from the horizontal and the x-ray beam vertical to the film, a routine AP film of the abdomen is made.

(ii) With the patient standing upright a lateral film of the abdomen is made, using a filter for soft tissue detail.

(iii) With the patient standing upright a routine lateral film of the pelvis with the acetabuli superimposed is made. In this film a radio-opaque ruler is placed in the natal cleft, which permits AP measurements of the pelvis.

(iv) If a large gap exists between the fetal presenting part and the sacral promontory, a further film is made. With the patient supine on the table at 45° as in film (i), a lateral film is made so that the sacral promontory appears just below and posterior to the centre of an 11 x 14 inch (2.75 x 35 cm.) film.

In the interpretation of the films, any persistent gap between the fetal presenting part and the maternal pelvis of 2 cm. or more should lead to a suspicion of some degree of placenta prævia and one of 3 cm. or more is virtually diagnostic. If the fetal presenting part is at all well engaged and the crowning point as seen on the lateral film is below the level of the superimposed acetabuli, no major degree of placenta prævia can exist.

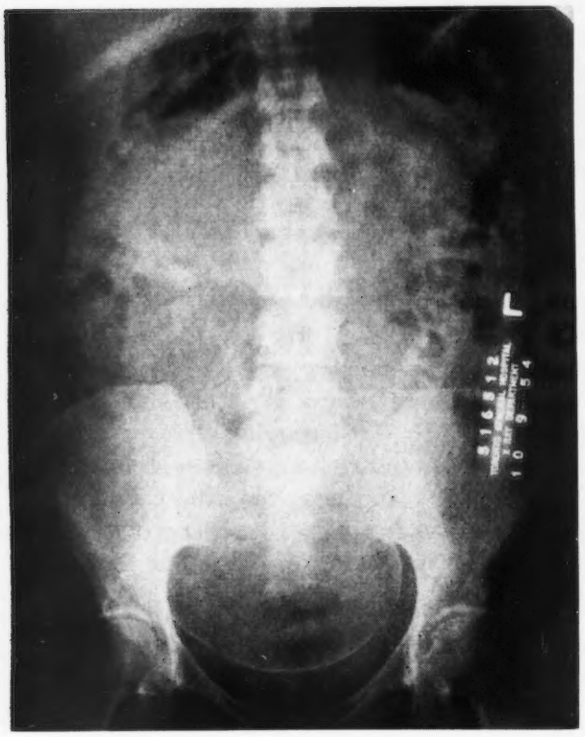
With careful technique, all cases may be placed in one of three categories:

(a) A major degree of placenta prævia. It should also be possible to localize the placenta as anterior, posterior or lateral.

(b) A minor degree of placenta prævia, the major portion being in the upper uterine segment.

(c) No placenta prævia.

Diagnosis is most accurate when the fetus lies longitudinally and when the head is presenting.



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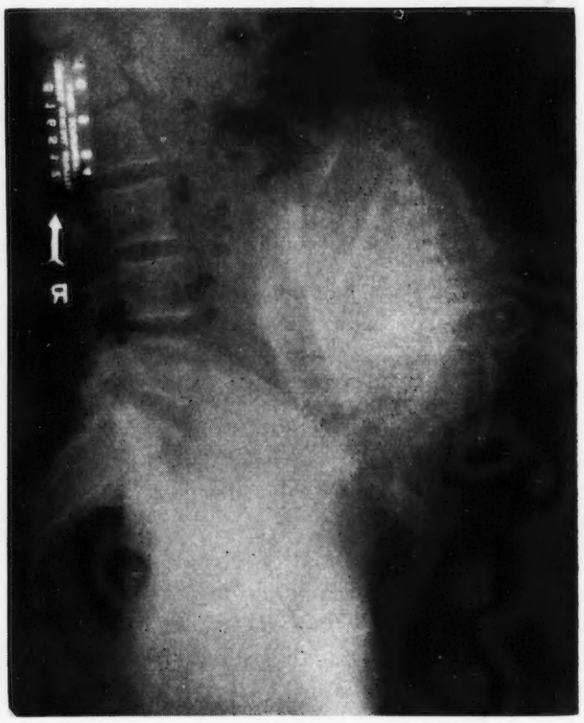

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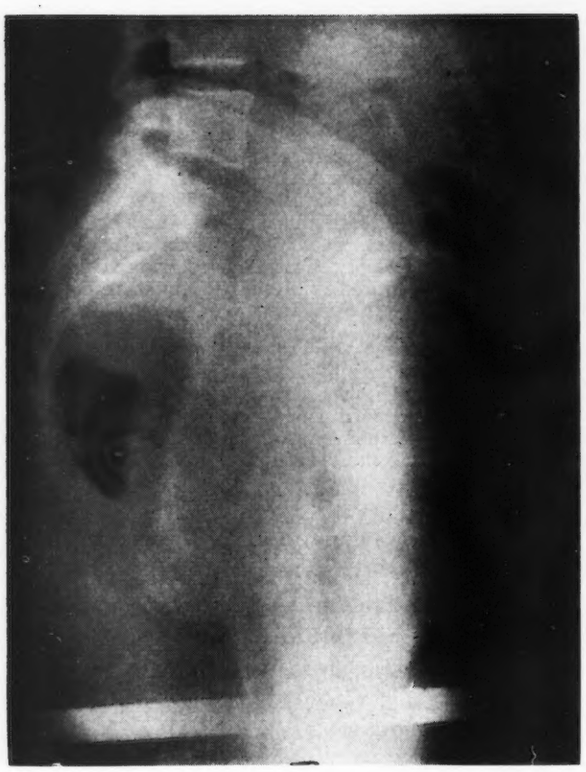


(C)

(D)

Fig. 1.—T.A. A case of complete placenta prævia, diagnosed radiologically at 34 weeks, confirmed at Cæsarean section at 36 weeks of gestation. (A) AP semi-erect film of abdomen. The head shows no significant lateral displacement. (B) Lateral erect film of abdomen. No placental shadow is seen within the uterine outline. (C) Lateral erect film of pelvis. The head is high and markedly displaced from the sacral promontory, but closely apposed to the symphysis pubis. (D) Lateral localized semi-erect film of sacral promontory region. The head remains high and does not gravitate towards the promontory.

In some abnormal presentations or normal presentations before the 32nd week of gestation the gravitational method may not be satisfactory. In these cases retrograde femoral arteriography is used to outline the placental site. Stallworthy[11] has emphasized the clinical value of the gravitational method.

RESULTS

In 69 cases of bleeding in the third trimester of pregnancy investigated radiologically by the gravitational method there were no major errors in diagnosis (see Table I). In 17 cases with a final diagnosis of placenta prævia there were 2 minor errors. One, a case diagnosed as a complete placenta prævia radiologically at 32 weeks, was found at term to have a low implantation. In the other, a diagnosis of no placenta prævia was made at term but at delivery it was felt that the placenta was situated as a low implantation.

TABLE I.

RESULTS IN THE RADIOLOGICAL DIAGNOSIS OF PLACENTA PRÆVIA IN 69 CASES OF BLEEDING IN THE THIRD TRIMESTER OF PREGNANCY

Total		*Placenta prævia*	*No placenta prævia*
Cases	69	17	52
Major error	0	0	0
Minor error	4	2	2
% accuracy	94.2	88.2	96.1

There were two minor errors additionally where a partial placenta prævia was diagnosed by radiography, but at delivery no evidence of this could be found.

These minor errors had no significant effect on the result in the various cases. The over-all accuracy of x-ray diagnosis in these cases was 94.2%. It is interesting to note the period of gestation at which it was possible to establish the diagnosis of placenta prævia with the gravitational technique (see Table II). An arteriogram was used in only 2 of these cases, one at 29 weeks with a transverse lie and a complete placenta prævia, and a second at 30 weeks where the gravitational method was more effective in disclosing a minor degree of low implantation of the placenta. Of the 15 cases correctly diagnosed, 10 were diagnosed before 36 weeks and at least theoretically could be treated conservatively.

TABLE II.

THE NUMBER OF CASES OF PLACENTA PRÆVIA DIAGNOSED CORRECTLY AND WITH MINOR ERROR BY X-RAY EXAMINATION AT THE PERIOD OF GESTATION INDICATED

Weeks of gestation	*Correct diagnosis*	*Minor error*
28	3	
29	1	
30	2	
32	2	1
34	2	
36	2	
38	1	
40	2	1
Total	15	2

Twenty-five cases finally diagnosed as placenta prævia were examined vaginally at various stages of gestation in the last trimester of pregnancy. In these there were 3 major errors and 2 minor errors (see Table III). None of these errors contributed to a fatal outcome for the mother or child. The major errors were the inability to palpate a complete placenta prævia through the vaginal fornices in grossly abnormal presentations at 28 to 32 weeks. The minor errors were a failure to recognize a degree of low implantation of the placenta at 28 to 32 weeks.

TABLE III.

RESULTS IN DIAGNOSIS BY VAGINAL EXAMINATION AFTER ADMISSION TO HOSPITAL IN 25 CASES OF PLACENTA PRÆVIA

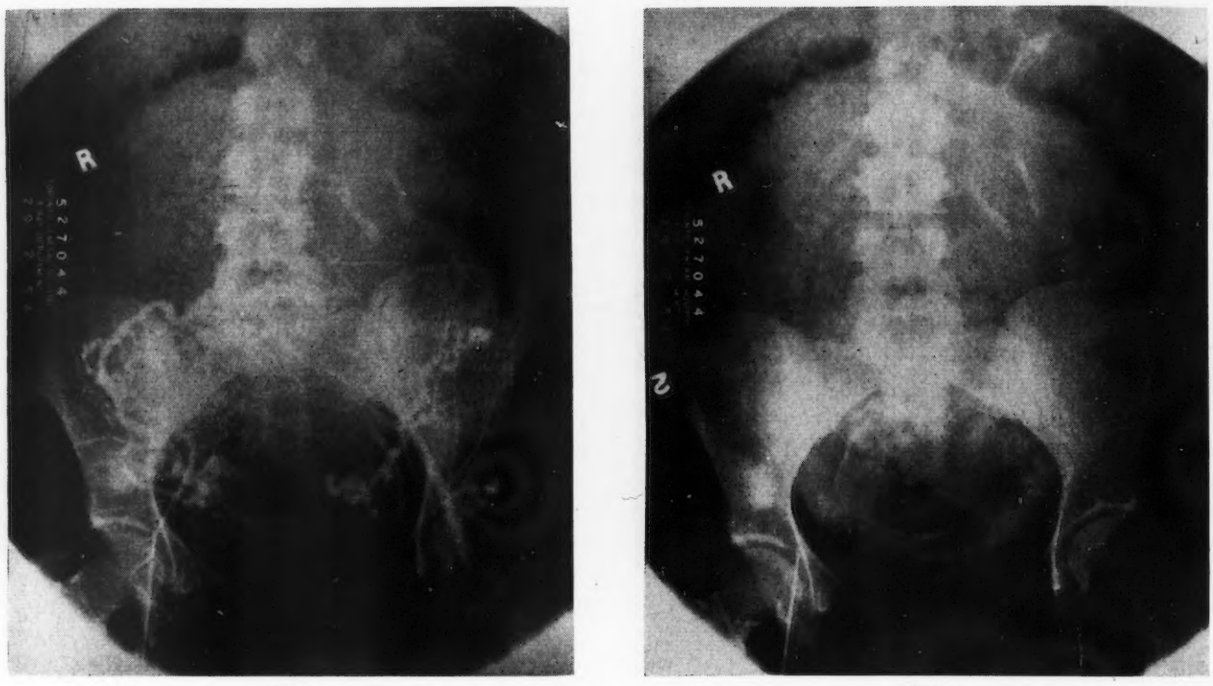
No. of cases of placenta prævia examined per vaginam	*Major errors*	*Minor errors*
25	3	2

Comparison of accuracy of diagnosis of placenta prævia by x-ray and vaginal examination (Table IV) shows that there were no radiological errors in diagnosis in complete or partial

TABLE IV.

A COMPARISON OF THE ACCURACY OF DIAGNOSIS IN TYPES OF PLACENTA PRÆVIA BY X-RAY AND VAGINAL EXAMINATION

Examination	*Complete*	*Partial*	*Low implant*	*Total*
X-ray				
Correct	10	2	3	15
Minor error			2	2
Vaginal				
Correct	7	9	4	20
Minor error			2	2
Major error	2	1		3



(A) (B)

Fig. 2.—A case of complete placenta prævia, diagnosed radiologically at 28 weeks, confirmed at Cæsarean section at 29 weeks of gestation due to persistent bleeding. (A) Placental angiogram. Arterial filling phase. Large tortuous branches of both uterine arteries are present in the pelvic cavity supplying a central placenta prævia. (B) Placental angiogram. Sinus filling phase. The placenta is clearly outlined by contrast medium within its sinuses.

placenta prævia, but that 3 errors were made in 19 cases on vaginal examination. All the errors in vaginal examination were made at periods of gestation from 28 to 32 weeks.

Of all the errors in diagnosis, only one was common to both x-ray and vaginal examination. This case at 32 weeks was diagnosed as a major degree of placenta prævia on x-ray, but no evidence of placenta prævia was found on vaginal examination. Subsequently at delivery a low implantation of the placenta was found.

In the 29 cases of placenta prævia treated on the public service, there were no maternal deaths; 5 infants (17.2%) were lost. If these are combined with the results on the private service, in a total of 81 cases of placenta prævia 10 infants (12.3%) did not survive. There were no maternal deaths.

DISCUSSION

It would appear that the x-ray method outlined is accurate in the diagnosis of placenta prævia. A high degree of accuracy was obtained in major degrees of placenta prævia both early and late in the last trimester of pregnancy. In addition, in cases of bleeding in the last trimester of pregnancy where a placenta prævia did not exist, radiography was found helpful in excluding it.

As might be expected, vaginal examination was inaccurate chiefly in recognizing major degrees of placenta prævia in the 28th to 32nd weeks, in the presence of a small fetus with an abnormal presentation. Minor errors in locating minor degrees of low implantation of the placenta were present in both techniques. These were of no clinical significance.

There is no reason to believe that one technique of examination replaces the other. Rather, the two are complementary. Where prolonged hospitalization is required, x-ray examination has been useful and accurate. Vaginal examination is useful in excluding lesions of the lower genital tract and in those cases of placenta prævia where expectant treatment is not indicated.

By carefully assessing the results of both forms of examination a higher degree of accuracy may be obtained than by either alone.

It is not intended to present the decrease in fetal mortality as significant, as the series is too small. However, the trend in these figures is encouraging.

CONCLUSIONS

1. The gravitational method of placental localization, supplemented in some cases by arteriography, has proven to be accurate in 69 cases of bleeding in the last trimester of pregnancy.

2. In 17 cases of placenta prævia, it was associated with only 2 minor errors and was particularly useful in 12 cases of major degrees of placenta prævia.

3. This x-ray technique gave correct results in all 10 cases of placenta prævia investigated between 28 and 34 weeks of gestation.

4. Vaginal examination is inaccurate in locating a placenta prævia where a small fetus and an abnormal presentation are present.

5. The most accurate diagnosis of placenta prævia is obtained when the results of both x-ray and vaginal examination are combined.

SUMMARY

Sixty-nine cases of bleeding in the last trimester of pregnancy were investigated radiologically for placenta prævia. The accuracy of this investigation was 94.2%, with no major errors and 4 minor ones. In investigating 17 cases of placenta prævia only 2 minor errors were made. Of 10 cases of placenta prævia occurring before 34 weeks, the diagnosis was accurately established by x-ray.

Vaginal examination in 25 cases of placenta prævia showed 3 major and 2 minor errors in locating the placenta. All these errors occurred in pregnancies between 28 and 32 weeks.

By combining these two methods of placental localization, a greater degree of accuracy may be obtained.

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RÉSUMÉ

Les auteurs de cet article rappellent les différentes statistiques de mortalité fœtale dans le placenta prævia, et les comparent aux chiffres obtenus dans les salles publiques de l'Hôpital général de Toronto. Un système basé sur l'admission de toutes les malades présentant des hémorragies vaginales pendant le troisième trimestre est exposé. Les précautions observées comprennent une réserve de sang à transfuser, la localisation radiologique du placenta et l'examen vaginal dans une salle d'accouchement équipée pour intervention césarienne d'urgence.

La technique radiologique de localisation du placenta est décrite en détail. Les auteurs ont eu recours à un artériogramme dans deux cas de leur série de dix-sept. L'examen vaginal, dans vingt-cinq cas, localisa incorrectement le placenta cinq fois, alors que la radiographie n'avait commis que deux erreurs sur dix-sept cas. Les auteurs suggèrent la combinaison des deux méthodes afin d'améliorer le degré de précision. M.R.D.

KERATO-ACANTHOMA*

A LESION SIMULATING CARCINOMA OF SKIN

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H. K. FIDLER, M.D.,‡ *Vancouver*

DURING THE PAST four or five years there has been an increasing recognition in the British and American literature[1-5] of a skin lesion originally called molluscum sebaceum in 1936 by MacCormac and Scarff[6] and more recently designated kerato-acanthoma, as suggested by Freudenthal.[1] A similar and possibly identical lesion known as "multiple self-healing squamous-cell epithelioma" is included in some of these papers.[2, 5, 7] The cases we have studied all had single lesions. We prefer the term kerato-acanthoma as being most descriptive and also because it avoids confusion with a somewhat similar but unrelated condition—"molluscum contagiosum".

It is the purpose of this paper to present our experience with 30 cases of kerato-acanthoma. Heretofore, many of these would have been considered low-grade squamous-cell carcinomas, both clinically and histologically. Evidence re-

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Fig. 1.—Kerato-acanthoma of nose. Male aged 75 years. Lesion present three weeks.

garding the benign nature of the lesion is presented, and details of six cases are described in which spontaneous healing followed partial biopsy only.

INCIDENCE

The incidence of kerato-acanthoma is hard to ascertain because of the past and present confusion with low-grade carcinoma and possibly certain types of focal pseudo-epitheliomatous hyperplasia.[5] During a 21-month period from February 1, 1954, we saw 77 cases of squamous-cell carcinoma of skin and 288 cases of basal-cell carcinoma. Thus the incidence of kerato-acanthoma was more than one-third that of squamous carcinoma and one-tenth that of basal-cell carcinoma. This incidence is very similar to that in 76 cases reported by Beare[1] from Belfast.

Both sexes are affected; in our small series 18 cases were in males and 12 in females. The highest incidence falls in the age group between 55 and 65, but cases are described from the mid-twenties to the middle of the tenth decade. In our cases the ages varied between 30 and 95 years, with an average of 60 years.

CLINICAL CHARACTERISTICS

Nineteen of the tumours were on the face and one was on the ear. Seven were on the dorsum of the hand, two on the forearm and one on the knee. The commonest site, however, is about the nose and cheeks.

The lesion commences as a small, raised, hemispherical nodule in the skin. Rapidity of growth is a striking feature. Within eight to 12 weeks it usually reaches its maximum size of about 1 cm. In our series, lesions ranged from 0.3 cm. to 2.5 cm. at the time of biopsy. The nodule itself is usually pinkish, or sometimes red. The skin at the edges of the tumour is pale as it becomes stretched over the firm nodule. In the central elevation, the lesion becomes scaly, crusted, friable and eventually may become excavated. At this stage the lesion resembles squamous or basal cell carcinoma (Figs. 1 and 2) and a biopsy is usually done.

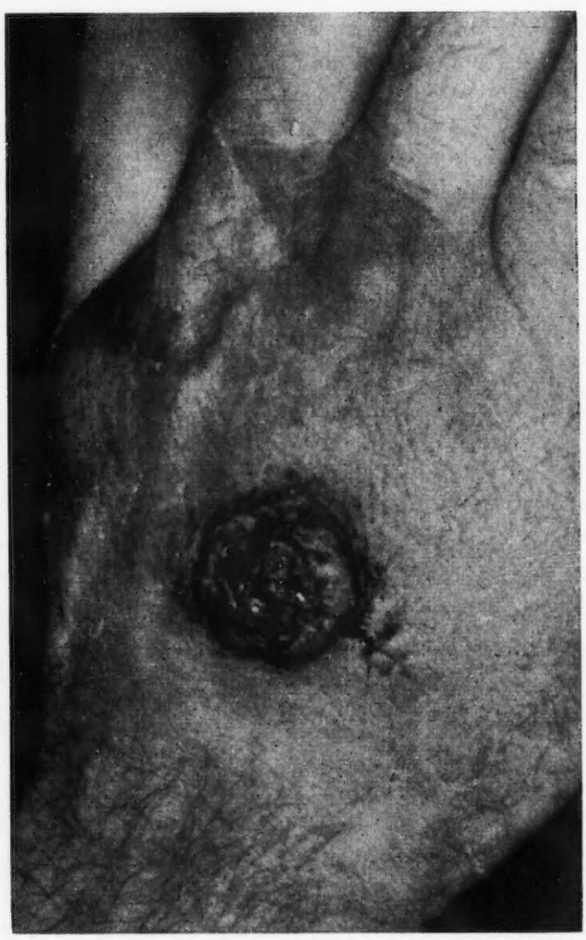

Fig. 2.—Kerato-acanthoma on dorsum of hand. Male, 66 years. This lesion developed to 2 cm. in size in three weeks following a cigarette burn.

The biopsy has certain fairly diagnostic histological features but it too may easily be mistaken for squamous-cell carcinoma. An essential aid in diagnosis is the history of rapid growth from inception. Ten of our patients had biopsies within four weeks of the onset of their lesions, and 21 within eight weeks. The largest lesion had been present only four weeks. The greatest duration was 25 weeks. Beare[1] reports two cases of one year's duration but this is certainly not the rule.

After a variable stationary period of some weeks the lesion spontaneously regresses in size. The eventual result is a small, pitted scar which is all that remains of a once apparently malignant growth. This natural regression and disappearance is a difficult matter to assess, for, rightly enough, the patient and physician are ill at ease without a biopsy or excision.

HISTOLOGICAL CHARACTERISTICS

The lesion has a characteristic pattern, particularly when studied under the low power of the microscope (Fig. 3). At the edge, relatively normal epithelium is raised towards the crater of the lesion and then becomes sharply undercut by a down-growth of hyperplastic epithelium in a manner somewhat resembling that of molluscum contagiosum. The bulk of the lesion is a focal, fusiform, poorly circumscribed proliferation of down-growing pegs of epithelium surmounted by papillary outgrowths and a keratinous cap that is usually depressed in crater fashion. Pegs of epithelial cells may appear confined by a limiting basement membrane, but more often these tail off into the stroma in a manner resembling infiltrating squamous-cell carcinoma. Indeed, most of the lesions we have studied present this appearance of invasion to such a degree that we are not convinced that a confident differential diagnosis between this lesion and squamous-cell carcinoma can be made from the deep margin alone. On the whole, however, the cells are better differentiated than in carcinoma, and in the words of Fouracres and Whittick[2] "there is an appearance of benignity that is difficult to define but which is due probably to its regularity of structure, relatively superficial position in relation to its size, and a completeness of differentiation of the hyperplastic epithelium". There is often a marked chronic inflammatory response in the adjacent stroma, and as the lesion becomes older, isolated foci of

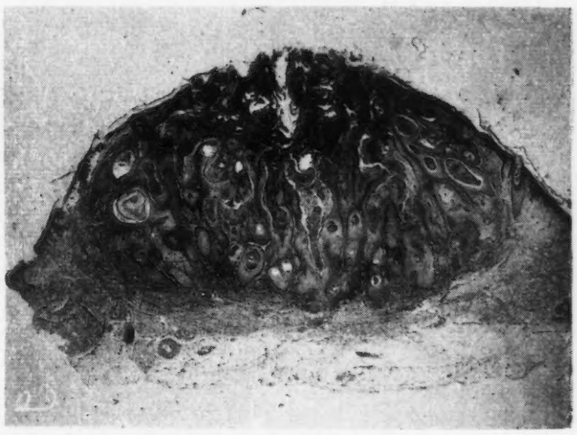

Fig. 3.—Excised kerato-acanthoma from forearm. Male aged 60 years. This lesion reached a size of 1.5 cm. in 6 weeks. (× 5).

epithelial cells undergo degenerative changes and are surrounded by intense lymphocytic infiltration and occasionally multinucleated foreign-body giant cells. The regressive changes in the pegs and islands of epithelial cells and the concomitant inflammatory reaction appear to be a healing response in the lesion.

Despite the histological similarity of this lesion to well-differentiated squamous-cell carcinoma, we believe that the differential diagnosis is relatively simple when a full excision biopsy specimen is available for study. Difficulties in diagnosis are increased when only a punch or wedge biopsy from the edge of the lesion is available for examination. If the biopsy specimen is well chosen to show the characteristic undercutting of proliferating epithelium joining at an acute angle completely normal epithelium at the edge of the crater, one is justified in suggesting the diagnosis of kerato-acanthoma. The accompanying clinical features of the characteristic appearing lesion with rapid growth over a short period of weeks make the diagnosis practically conclusive.

The proof of histological diagnosis lies in those cases in which only a biopsy has been performed and the lesion has ultimately regressed spontaneously. Fouracres and Whittick[2] report seven cases which after biopsy diagnosis were untreated and allowed to run their natural course to spontaneous regression. Six of our cases had only biopsy and without further treatment spontaneously healed. Details of these cases follow.

CASE REPORTS

CASE 1.—Mr. P., aged 61 years, had a lesion 1 cm. in diameter on the dorsum of his hand which had been present four weeks. He dated the onset of his condition

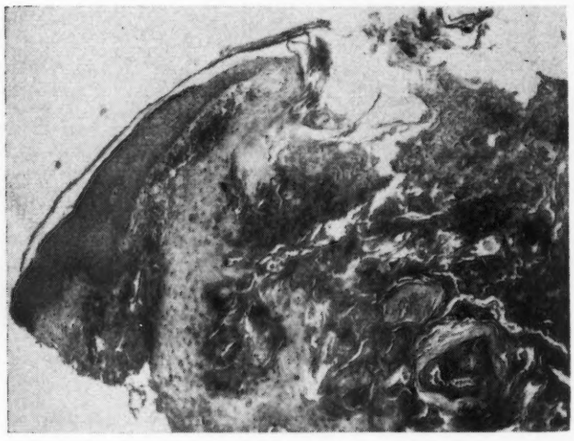

Fig. 4. (Case 2).—Biopsy from edge of lesion showing normal epithelium approaching the crater edge, with a sharp undercutting by proliferating epithelium. (× 35).

from a barnacle abrasion. When he was seen by his physician, approximately one-eighth of the lesion was removed for histological study. No further treatment was undertaken. Six weeks from the time the lesion was biopsied, the tumour had almost completely disappeared. When he was seen seven months later, the lesion had completely disappeared, and a small, almost imperceptible scar remained.

CASE 2.—Mrs. H., aged 67 years, consulted her physician about a lesion on her right cheek which measured 0.5 cm. in diameter, and had been present for four weeks. This tumour was punch biopsied (Fig. 4) and no further treatment was given. Four weeks later the lesion had completely disappeared and all that remained was a small erythematous pit at the site of the tumour.

CASE 3.—Mr. T., aged 56 years, had a lesion 0.5 cm. in diameter, which had been present on his left forearm for two weeks. A small portion of the tumour was removed for microscopic examination (Fig. 5) and no other treatment was given. There was no evidence of the lesion after two months; all that remained was a small, white, depressed scar.

CASE 4.—Mrs. C., aged 48 years, was seen by a dermatologist who felt that the lesion was characteristic clinically and took a punch biopsy specimen. This lesion was on the left forehead, near the hair line, measured 0.6 cm. in diameter and had been present for 18 weeks. The patient was not seen again for some time, but several months later the lesion had disappeared and there was no evidence of any recurrence.

CASE 5.—Mr. J., a 28-year-old male, had had a lesion 1.5 cm. in diameter on the dorsum of his hand for four weeks. A small biopsy specimen was taken through one edge of the tumour and no further treatment was given. The patient was not seen for some months, but one year after the biopsy the lesion had completely disappeared and there was no evidence of recurrence.

CASE 6.—This 95-year-old farmer stated that the lesion appeared on the right side of his nose over a period of two months following a pinching injury. The lesion was a raised, firm area, measuring 1 cm. in diameter, which was clinically felt to be a cystic basal-cell carcinoma. A small biopsy was performed and reported as kerato-acanthoma (Figs. 6 and 7); no further therapy was undertaken. When seen one month later, the lesion was about one-third its original size, and had completely disappeared 2½ months after the biopsy.

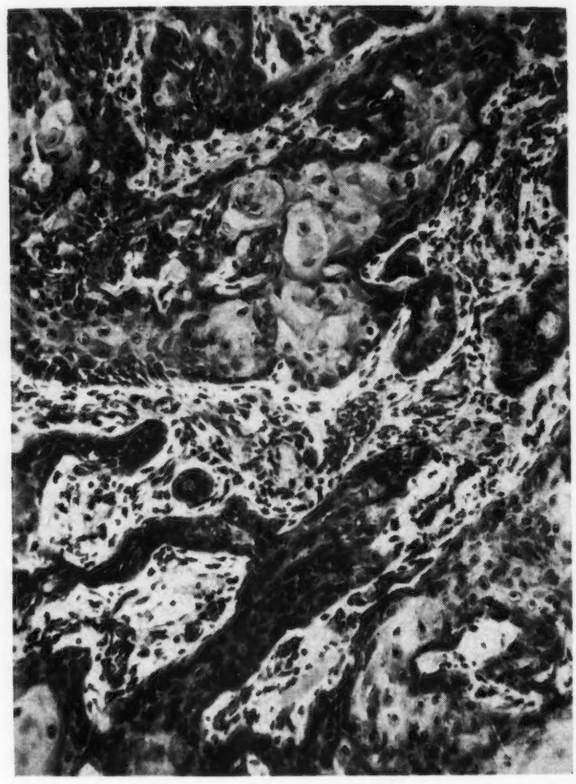

Fig. 5. (Case 3).—Biopsy showing a deep part of the lesion which simulates low-grade squamous-cell carcinoma. (× 125).

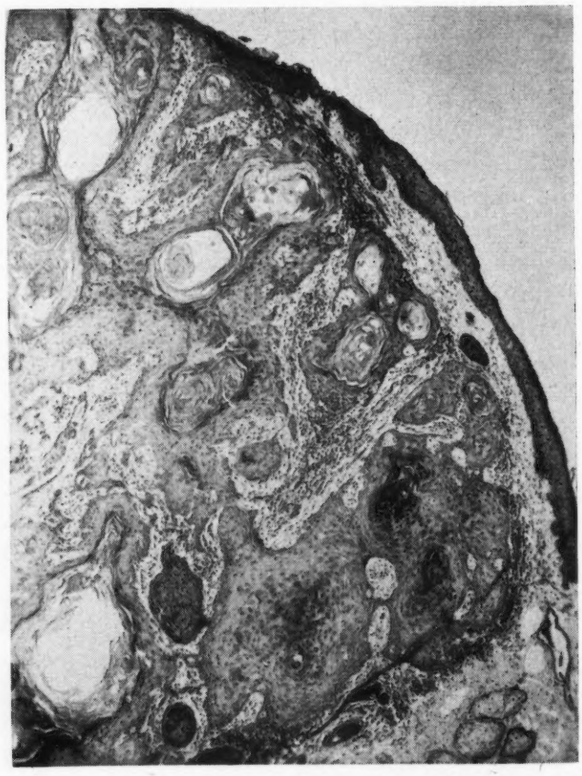

Fig. 6. (Case 6).—Biopsy from edge of kerato-acanthoma. (× 35).

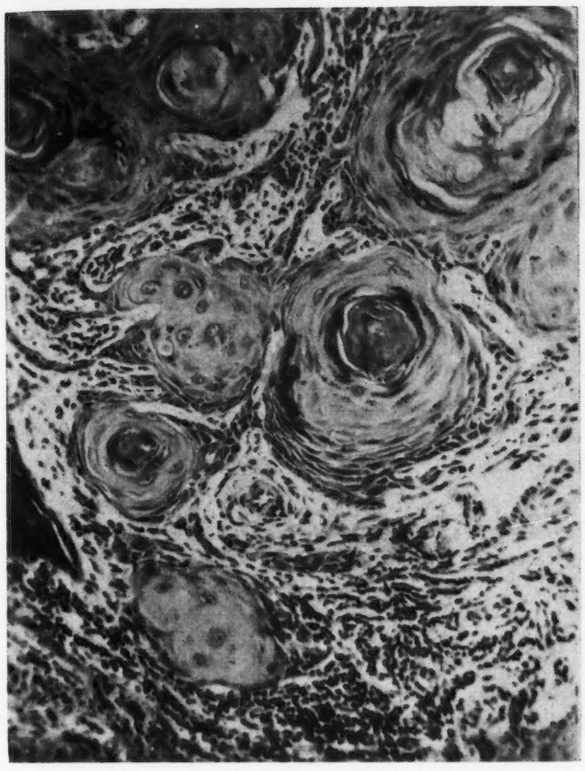

Fig. 7. (Case 6).—High power magnification of deepest part of the lesion depicted in Fig. 6, showing an appearance simulating low-grade infiltrating squamous carcinoma. (× 125).

Eight of our cases have been seen too recently for adequate follow-up, but in none of the others has there been any evidence of recurrence up to the time of writing. In addition to the six cases outlined above in which spontaneous regression took place after a small biopsy only, two were electrocauterized after biopsy, two had excision biopsies followed by electrocautery, and the remaining cases had an excision biopsy alone.

COMMENT

Recognition of kerato-acanthoma is of practical importance since the prognosis and therapy differ from that of squamous carcinoma. There is no doubt that many of these lesions have been diagnosed in the past as carcinoma and treated as such. The relatively good results of treatment of squamous carcinoma of the skin are due, in part, to the inclusion of these non-malignant lesions in reported series.

The histological criteria for the diagnosis of kerato-acanthoma leave much to be desired. In the early part of our study of these cases, we requested excision biopsies of the entire lesion because in most instances we were not entirely convinced of the benignity of the lesion. With more experience and the assurance afforded by observing the natural regression of some of these lesions, we now believe that examination of a well-chosen biopsy from the edge is usually practically diagnostic.

Various types of therapy have been advocated including x-ray, radium implants, podophyllin, electrocautery, silver nitrate cautery, Mapharsen, and surgical excision. In most instances we feel that excision is the treatment of choice as it allows histological study of the complete lesion, and moreover the resulting scar is usually less disfiguring than the scar remaining from a spontaneously healing lesion. There will be a number of cases in which the clinical and/or biopsy findings are inconclusive and the patient is probably best served by treating the lesion as if it were a low-grade squamous carcinoma.

The etiology of the condition is not known. The rapid evolution and other features have suggested the possibility of a virus infection. Inoculation attempts to prove an infective nature have not been successful.[1, 3] Trauma frequently precedes development of the lesion.

CONCLUSIONS

1. Kerato-acanthoma is a relatively common benign skin tumour characterized by rapid growth followed by spontaneous regression and disappearance.

2. The usual sites are face and hands, but the ears, forearms, legs, and other sites are occasionally involved.

3. The diagnosis is made by correlating the clinical appearance and course with the histological appearance on biopsy. Careful assessment of these features will, in most instances, differentiate kerato-acanthoma from squamous carcinoma with which the lesion has been confused in the past.

4. Thirty cases of kerato-acanthoma are presented in which six had partial biopsies only and regressed spontaneously.

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Résumé

Depuis quelques années, la lésion cutanée jadis désignée sous le vocable de "molluscum sebaceum" a pris de l'ampleur dans les milieux dermatologiques. Connue maintenant sous le nom de "kérato-acanthome", les auteurs l'ont rencontrée également dans les deux sexes, surtout vers la soixantaine, mais dix fois moins fréquemment que le carcinome baso-cellulaire. L'endroit de prédilection est le nez et les joues. La lésion croît rapidement et présente au microscope une apparence qui ressemble de près à celle de l'épithélioma pavimenteux. Après quelques semaines, elle diminue spontanément de volume et laisse une petite cicatrice déprimée. Six cas sont présentés en exemple. Les auteurs recommandent l'excision comme traitement de choix, permettant l'examen histologique complet et laissant une cicatrice plus acceptable que celle de la régression spontanée. M.R.D.

TREATMENT OF STAPHYLOCOCCAL EMPYEMA IN CHILDREN*

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An increasing incidence of staphylococcal infections has been noted in recent years throughout the country. Young children and newborns are particularly susceptible to the staphylococcus. One of the most serious of these infections, from the standpoint of both morbidity and mortality, is empyema. It is the purpose of the authors to record a program of treatment which appears to have considerable merit in staphylococcal empyema.

Clinical Record

Ten patients were treated in the first four months of 1955. Their ages ranged from three weeks to 11 years. Eight patients were under two years of age. Of these, five (50%) were under three months of age. The left pleural space was involved in five cases and the right side in the same number. There were no bilateral cases.

Although diagnosis, epidemiology and etiology are not included within the scope of this paper, several points bear emphasis. All patients had a history of an ordinary upper respiratory infection which suddenly changed into a serious illness. This suggests that the staphylococcus was a secondary or synergistic invader, as has been recorded in epidemic influenza.[1] In three cases a presumptive source of infection was found. In one there was a staphylococcal omphalitis, in one an impetigo and purulent otitis media, and in one the mother had perineal staphylococcal abscesses in the postnatal period.

Before the empyema was clinically or radiologically demonstrable, an extreme gaseous distension of the entire bowel was noted in most cases. The abdominal distension persisted for some days. During the first 24 or 48 hours, an erroneous diagnosis of bowel obstruction has been reported.[2] It should be noted that patients with staphylococcal empyema and pneumonia do not as a rule have vomiting or diarrhœa, unlike those with an acute abdominal condition. In fact, all patients treated received systemic medication orally. The signs of empyema developed so rapidly that the true diagnosis was not long in doubt.

Treatment

Treatment in recent years usually has consisted of multiple needle aspirations of the chest with instillation of antibiotics. However, in many instances the disease became chronic and further surgical procedures such as rib resection or lung decortication became necessary. As a result, morbidity was prolonged, and frequently, when the infection was finally controlled, the lung was ensheathed in a mass of scar tissue.

In the ideal management of any disease, one should attempt rapid and complete control of the disease process with preservation of as nearly normal function of the involved organ as possible. In the application of this ideal to empyema, the following principles might be considered of prime importance:

(a) Early control of infection.
(b) Early evacuation of the pleural space.
(c) Early re-expansion of the lung.

*Presented to the Annual Meeting of the Royal College of Surgeons, Quebec City, October 1955.

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Keeping these points in mind, a regimen of treatment was adopted in the handling of 10 cases of staphylococcal empyema in young children (Table I).

TABLE I.

Important Points in the Treatment of Empyema
(a) Early intercostal drainage
(b) Continuous suction
(c) Local antibiotics and Varidase (streptokinase + streptodornase)
(d) Systemic antibiotics
(e) Early removal of the drainage tube

1. Early intercostal drainage was carried out. As soon as the diagnosis of empyema was suspected, needle aspiration of the chest was performed. If pus was encountered, a size 20-24 F intercostal catheter was immediately inserted under local anæsthesia. This was a minor procedure done on the ward, without rib resection. The catheter, in addition to providing an outlet for the pleural exudate, allowed easy and frequent intrapleural medication.

2. Continuous low-pressure intercostal suction was applied to the catheter. The suction machine consisted of a Steadman pump with a mechanism devised to deliver a negative pressure of 10-15 cm. of water and to prevent build-up of pressure beyond that level. The suction was continuous, except for a period of 1-2 hours after instillation of drugs through the catheter four times daily.

3. Intrapleural instillation of drugs was immediately instituted. In some cases penicillin and streptomycin, in some a solution of chloramphenicol (the intramuscular product) and in one case a solution of intravenous erythromycin was injected through the catheter. This was done every 12 hours. In every case sensitivity tests demonstrated resistance of the staphylococcus to penicillin and streptomycin. However, there was no noticeable clinical variation in those cases treated with penicillin and streptomycin intrapleurally, compared with those in which wide-spectrum antibiotics were used. It is possible that with an exceedingly high concentration of penicillin and streptomycin obtained in a small closed space, a bactericidal effect was exerted in spite of the inability of laboratory tests to demonstrate this.

Another point of concern to the bacteriologist is that laboratory sensitivity testing of penicillin against the staphylococcus is open to quantitative error. The *in vitro* test for penicillin sensitivity measures penicillinase production by the organism in question. However, penicillinase may be produced very slowly at the onset of infection, and initially the staphylococcus may be clinically sensitive to penicillin in spite of demonstrated *in vitro* resistance.

The staphylococcus stimulates production of an exudate high in fibrin content. The fibrin in the pus is responsible for the loculation frequently seen so early in staphylococcal empyema. The tendency to loculation can be counteracted in two ways: (a) by early and effective drainage before the pus has become thick; (b) by the use of the enzymes streptokinase and streptodornase to destroy the fibrin and allow evacuation of the resultant thin pus by suction. Streptokinase, 50,000 units, and streptodornase, 12,500 units in 10 c.c. of solution, was instilled into the chest every 12 hours through the intercostal drain. The enzymes were alternated on a six-hourly basis with the antibiotics. After each instillation, the intercostal catheter was clamped for a period of 1-2 hours.

It should be noted that in no case was a fibrin plug encountered in the lumen on removal of the intercostal catheter. The formation of plugs in the catheter was probably prevented by the combination of enzymatic digestion of fibrin plus the irrigating effect of frequent instillation of fluid through the catheter.

4. In each instance, the patient was desperately ill. Systemic antibiotics were given in large doses to combat the primary pneumonia as well as the empyema. Sensitivity tests in most cases showed the staphylococcus to be susceptible to both erythromycin and chloramphenicol. Initially all patients received oxygen therapy. Six patients received blood transfusions and three patients received staphylococcal antitoxin. It is difficult to assess the relative merit of each aspect of treatment. However, we are quite convinced that drainage and complete evacuation of the pleural space is of foremost importance.

5. The drainage tube was removed as soon as it was felt that its purpose had been served. In the past, intercostal drainage tubes used in the treatment of empyema were usually left in place for prolonged periods and removed

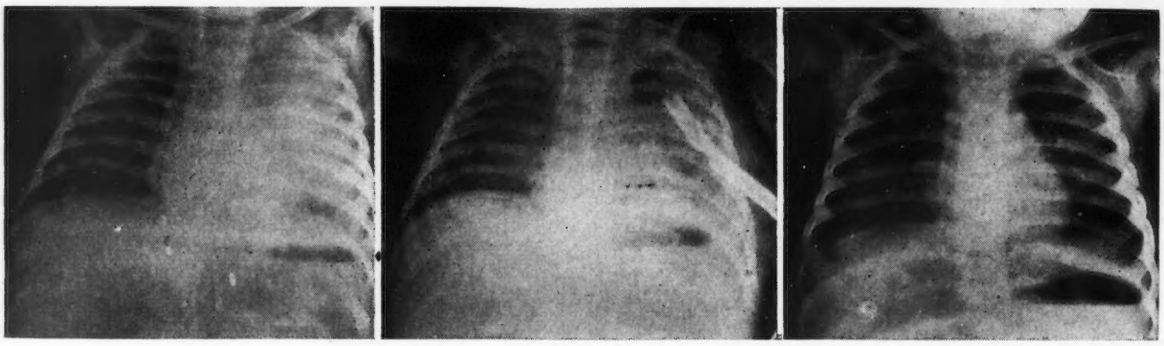

Fig. 1a Fig. 1b Fig. 1c

Fig. 1.—Radiographs depicting progress in Case 1 (D.R.): (a) before intercostal drainage; (b) on the third day following intercostal drainage; (c) final result one month after treatment was begun.

only very gradually. In this series of cases, in most instances, the tubes were removed in from six to 14 days. The following factors were used as a guide to determine the proper time for removal of the tube: (a) normal temperature; (b) cessation of intercostal drainage; (c) roentgenographic evidence of a clear pleural space. When the aforementioned conditions prevailed, the intercostal tube was removed and measures were taken to prevent any air leak back through the tract of the tube.

Results

Ten cases of staphylococcal empyema in children were treated according to the regimen outlined. Six patients recovered without complications of any type (Table II). In these, the average duration of hospitalization following intercostal drainage was 19 days and all had recovered completely on discharge from hospital (Fig. 1). Complications developed in four children (Table III).

Staphylococcal enteritis was seen in one infant. This was controlled readily by discontinuing erythromycin and administering neomycin for a short period. The second complication was seen in an infant discharged from hospital 19 days after drainage. The following day, the baby developed fever and was re-

TABLE II.

Uncomplicated Cases

Patient and age	*Hospital days after drainage*
D.R.—6 months	20
T.E.—3 weeks	12
D.D.—4 years	17
J.W.—3 months	28
M.B.—22 months	21
R.L.—11 years	18

TABLE III.

Complicated Cases

Patient and age	*Complication*	*Hospital days after drainage*
D.L.—2½ months	Diarrhœa	31
R.B.—1 month	Residual drainage from catheter tract	27
J.T.—1½ months	Unexpanded lung	24
C.G.—1 month	Bronchopleural fistula	60

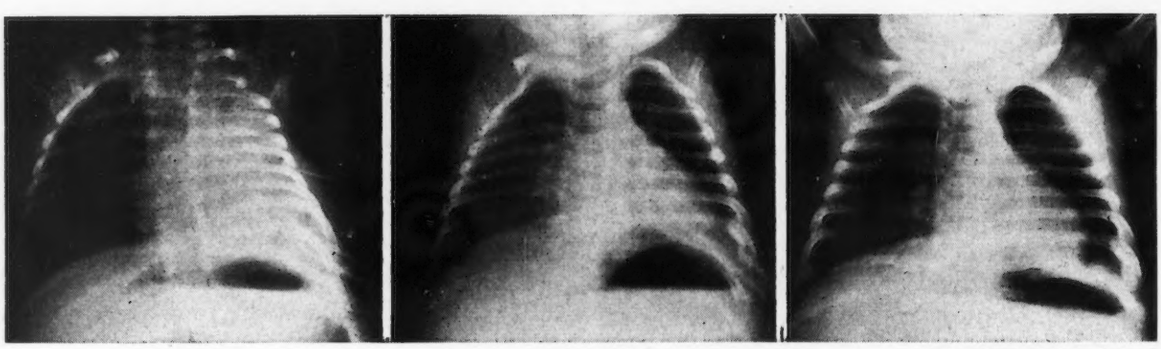

Fig. 2a Fig. 2b Fig. 2c

Fig. 2.—Radiographs of J.T. showing: (a) persistent atelectasis 12 days after intercostal drainage was performed; (b) re-aeration of lung following expulsion of obstructing mucus plug; (c) appearance of chest one week after removal of intercostal catheter.

admitted to hospital. A small quantity of seropurulent material drained spontaneously from the catheter tract and the baby recovered without further incident.

In a third infant, drainage had ceased and the temperature was maintained at a normal level in 12 days following drainage. In spite of that, there was still no evidence of lung expansion. However, the course of events over the next few days proved that the empyema had been completely controlled and the lung still remained atelectatic. Intratracheal suction with a small catheter was carried out at frequent intervals and this procedure stimulated the baby to cough out a large thick plug of mucus on one occasion. Soon after this, there was clinical evidence of air entering the lung, and roentgenograms taken a few days later revealed a very well expanded lung (Fig. 2). Recovery was not further complicated in this infant.

In a fourth case, the baby did well after treatment. The temperature remained normal after 10 days and the pleural space was clear. The intercostal tube was removed in 12 days. However, following this, air began to collect in the pleural space because of a bronchopleural fistula. A tension pneumothorax developed and the intercostal drain was reinserted. With the aid of suction, the lung was well expanded in 24 hours. The tube was removed 12 days later and over the next few days a tension pneumothorax again developed. After re-insertion of the catheter and the use of constant suction for a third time, the lung quickly expanded and it was possible to remove the drain in 12 days without further trouble.

Discussion

In this group of 10 cases treated by the method outlined, the results of treatment have been most encouraging. The duration of illness and hospitalization has been reduced to a minimum. The need for further surgical procedures such as rib resection or decortication has been avoided.

The lung in every case on discharge from hospital was well expanded and the pleural space was relatively normal. One might even suspect that at least in some of the patients a free pleural space results as evidenced by the tension pneumothorax with complete collapse of the lung in one instance. There has been no mortality in children treated by this means. However, no case of fibrocystic disease of the pancreas has been encountered in this group.

Summary

In summary, it is proposed that staphylococcal empyema be treated in the following manner.

1. Immediate intercostal catheter drainage with local anæsthesia.
2. Application of low-pressure suction to the catheter.
3. Regular intrapleural instillation of antibiotics and of streptokinase and streptodornase solution, followed by temporary interruption of suction.
4. Systemic administration of antibiotics in large doses, along with such ancillary measures as may be indicated.
5. Removal of the drainage tube when the following conditions prevail: (a) maintenance of a normal temperature; (b) cessation of drainage from the chest; (c) evacuation from the pleural space of pus, fluid and air.

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EFFECT OF CHLORPROMAZINE ON CEREBRAL HÆMODYNAMICS AND CEREBRAL OXYGEN METABOLISM IN MAN

The cerebral hæmodynamic effects of chlorpromazine administered intravenously and intramuscularly were observed in 13 subjects by Moyer and his colleagues (*Circulation*, 14: 380, 1956). Cerebral blood flow was frequently reduced after intravenous administration of chlorpromazine, but apparently this change was a result of the associated reduction in mean arterial blood pressure rather than a direct effect of the drug on the cerebral circulation. When the blood pressure was then elevated to normotensive levels with norepinephrine, the cerebral blood flow returned toward normal. Chlorpromazine did not exert a direct depressant effect on cerebral oxygen consumption. When chlorpromazine was given intramuscularly, blood pressure was not reduced significantly, and cerebral blood flow and cerebral oxygen consumption were not altered. The metabolic effect of chlorpromazine is therefore quite different from that of morphine and barbiturates, since the latter agents depress cerebral oxygen uptake without affecting cerebral blood flow.

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RESULTS OF INSTITUTIONAL TREATMENT OF JUVENILE MENTAL DEFECTIVES OVER A 30-YEAR PERIOD

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THE PURPOSE OF the present investigation is assessment of the results of institutional treatment of juvenile mental defectives in the Province of Alberta, between 1922 and 1952.

Patients referred to the Provincial Training School, Red Deer, are normally accepted between the ages of five and 16 years. Despite continuous growth to a present bed-capacity of 700, there has always been a waiting period for admission of one or two years. No considerations of race, religion, or financial standing operate in the selection of cases, which come from a mixed rural and urban population over the entire area of the province.

Institutional facilities include trained nursing care; a modern school, which provides teaching to grade 6 under the direction of an educational psychologist; sense-training classes; occupational therapy; carpentry and cobbling; a farm villa and recreational instruction. The complete program has been in operation only since 1949. Before discharge, a varying period is spent on parole in selected employment, chiefly domestic or farm work. Under the laws of this province (1932), sterilization is carried out before any final discharge can be effected.

Of 310 total discharges since 1922, 47.1% were available for analysis, on an average follow-up period of 4.65 years. For the purpose of this investigation, the treatment is considered successful if the trainee has maintained his or her position in society without conflict leading to official interference.

GENERAL ANALYSIS

Our use of terms high-grade and low-grade, as applied to morons and imbeciles, is arbitrary, and defined specifically for easier assessment of group results in this paper. For example, borderline defectives are included in our high-grade moron category. Group definitions used are as follows: high-grade moron (70-85 I.Q.); low-grade moron (50-69 I.Q.); high-grade imbecile (40-49 I.Q.); low-grade imbecile (30-39 I.Q.); idiot (below 30 I.Q.).

The corresponding numbers of discharges in these I.Q. groups were: 56, 137, 51, 29, 18. In addition, there were 16 others of indefinite I.Q., and three found to have normal intelligence.

TABLE I.

SUCCESSFUL DISCHARGES
PER CENT KNOWN SUCCESSFUL 61.6

% success per I.Q. group:	50 - 59 I.Q. group 66.6%
80 - 85 I.Q. group 50%	40 - 49 I.Q. group 40%
70 - 79 I.Q. group 61%	30 - 39 I.Q. group 66.6%
60 - 69 I.Q. group 78%	< 30 I.Q. group nil
Mean I.Q. of successes 60	Mean I.Q. of failures 57
Average training period of successes.....	5.5 years
Average training period of failures.....	4.9 years

Of patients discharged 69% were sterilized. The remainder comprise a group consisting of extremes in subnormal I.Q., patients discharged before the Sterilization Act was passed, and patients discharged, for various reasons, before sterilization procedure.

Of discharged trainees 23% are known to have married. Of these, 94% were female. The average I.Q. of this group was 63, with a range of 42-85. Several of those married had an attempted surgical repair of the Fallopian tube. Several attempted adoption. At least one (I.Q. 59) successfully adopted and reared her child.

The comparison of success percentages for various I.Q. groups as shown in Table I indicates that the I.Q. alone is a variable factor in predicting successful treatment, granted always that the most favourable environment is made available for any particular case on discharge. Personality, attitude, and character, as well as age, training period, and I.Q., are ever-present contributory factors to ultimate success or failure.

The first two factors were not amenable to measurement in this investigation. It is with the remaining five variables that this work is concerned.

ANALYSIS OF MORONS

Maximum success has been attained with the 60-69 I.Q. group, while a significant falling-off

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in success is apparent in the high-grade moron (70-85 I.Q.) group (Table I).

In our opinion, low-grade morons are patently aware of their defect, accept it and are thereby able to effect a realistic adjustment on discharge. High-grade morons incline to deny their own disability and are never made fully aware of their limitations, perhaps through the constant encouragement they are given in institutional life to attain ends within their means but still well below the average child's attainment. Thereby they come to meet the world on equal terms, which they cannot in fact do.

It would seem necessary to demonstrate periodically to this group what they cannot do, as well as what they can do, with a view to improving their attitude to their defect.

TABLE II.

MORONS: DATA ON ADMISSION, TRAINING PERIOD AND DISCHARGE

			Years
Mean age on admission	70 - 85	I.Q. group	13
Mean age on admission	50 - 69	" "	15.75
Av. training period	70 - 85	I.Q. group	6
Av. training period	50 - 69	" "	4.4
Mean age on discharge	70 - 85	I.Q. group	19
Mean age on discharge	50 - 69	" "	20.15

High-grade morons begin training 2.75 years younger than those of low grade (Table II), and are therefore less time in contact with the outside environment to come to a certain realization of their disability, or develop means of compensating it. They spend 1.6 years longer in training in the protected environment of the institution, and are discharged, on the average, at an age at least one year younger than low-grade morons.

As a consequence of their earlier admission, high-grade morons have to cope with the entire period of their adolescent emotional development in an atmosphere of parental "rejection", i.e., institutionalization. This in itself tends to make compensation for their defect more difficult, and emotional immaturity is combined with their intellectual impairment.

Further evidence for this opinion can be found in a comparison of successes and failures within the group (Table III). High-grade moron failures are admitted at an age two years younger than successes within the group. They train 0.25 years longer, and are discharged 1.76 years younger, at an average age of 18.6 years.

A possible factor encouraging early institutionalization may be the unruliness of the failure group before admission. The incidence of character disorder in various groups is discussed separately, in a further section.

MORON FAILURES

It is noteworthy, in contrast to the preceding, that failures in the low-grade moron group had one year less training than the more successful of their genre, and were discharged 18 months earlier by age (Table III). The value of prolonging in-treatment for this group, at least until there is some proximity to the 21st birthday, seems indicated. It is not always possible to attain such a desirable goal, however. Constant pressure is exerted in certain cases, by parents, relatives and patients themselves, to gain quick discharge after a brief period of training. It takes the utmost in parent-school liaison to minimize this cause of failure.

TABLE III.

GENERAL FACTORS IN SUCCESS AND FAILURE

Mean training period, successes:		*Mean training period, failures:*	
	Years		*Years*
70 - 85 I.Q. group	6.26	70 - 85 I.Q. group	6.5
50 - 69 " "	4.85	50 - 69 " "	3.94
40 - 49 " "	7.1	40 - 49 " "	4.6
30 - 39 " "	6.6	30 - 39 " "	16.0
Mean admission age, successes:		*Mean admission age, failures:*	
70 - 85 I.Q. group	14.1	70 - 85 I.Q. group	12.1
50 - 69 " "	15.87	50 - 69 " "	15.18
40 - 49 " "	14.1	40 - 49 " "	16.8
30 - 39 " "	19.0	30 - 39 "	10.0
Mean discharge age, successes:		*Mean discharge age, failures:*	
70 - 85 I.Q. group	20.36	70 - 85 I.Q. group	18.6
50 - 69 " "	20.72	50 - 69 " "	19.1
40 - 49 " "	21.2	40 - 49 " "	21.4
30 - 39 " "	25.6	30 - 39 " "	26.0

The majority of unsuccessful morons find themselves committed to Provincial Mental Hospitals, where they are readily recognized as adult defectives. Certain of the males in the group appear as psychopathic personalities and criminal offenders, who ultimately fall into the recidivist category.

This tendency does not appear among the females of the group. From the evidence available, it appears that they are more likely to seek help and advice from welfare workers and

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guidance clinics, or by reapplication to the Training School, chiefly on account of personality disorders or neurotic symptoms.

IMBECILE AND IDIOT DISCHARGES

A definite correlation exists between success and length of training within the high-grade imbecile group (I.Q. 40-49). This tends to corroborate the value of training within this group, and reveals that failures within the group have had 2.5 years' less training.

Low-grade imbeciles (I.Q. 30-39) show a proportionate success equal to that of the over-all discharge group (Table I), with an average training period of 6.6 years. However, further training does not benefit the failures within this group, one-third of whom must be regarded as uninfluenced by present training methods. The idiot group are totally unresponsive.

A majority of high-grade imbeciles were discharged to their families, and the remainder into the care of households prepared to assume a foster-parent role. All low-grade imbeciles and idiots were discharged to their families.

It is interesting to record that six cases in the high-grade imbecile group married, and have apparently remained successful, with one exception, an epileptic girl, prone to irritability, who divorced her husband.

Whereas unsuccessful morons who were committed for further institutional care were treated for character disorders, psychoneuroses and recidivism, failed imbecile and idiot discharges show in mental hospital records with a marked incidence of psychoses, or as deteriorated epileptics. This tends to support the work of Le Vann,[1] in conceding a schizophrenic nucleus amidst the lower grades of mental defect.

In a study of the incidence of character disorder which now follows, we hope to indicate the wide extent of neurotic factors in the behaviour of higher grades of defective; and, indeed, to show that this neurotic substructure fades off at just the point where psychotic features become prominent, among the submoronic groups of mentally defective patients.

INCIDENCE OF CHARACTER DISORDER PRIOR TO ADMISSION

Character disorder has been taken to mean persistent misconduct trying the patience of society, or such that the parents themselves have declared the child beyond their control. It does not include masturbation, isolated minor sexual offences, or isolated instances of theft or aggressive behaviour. It does, however, include extreme single instances, such as murder.

The bulk of these disorders consist of repeated theft and assault, promiscuity, prolonged unruly behaviour and rowdyism. It is noteworthy that in no case has any male been charged with rape or attempted rape, or been involved in a heterosexual offence, before admission. On the other hand, a large proportion of females have been concerned in illegitimate births and promiscuity. This seems to indicate, not an overpowering sexual demand as a consequence of mental defect, since the males show no instance of it, but rather that female defectives are easy prey for the wiles and depredations of "normal" society, at a time when their character has been insufficiently fashioned to compensate the limitations of their intellect.

TABLE IV.

CHARACTER DISORDERS

Character disorder per I.Q. group	
	%
70 - 85 I.Q. group	66.6
50 - 69 " "	55.0
40 - 49 " "	54.2
30 - 39 " "	14.2

Character disorder, successes:		*Character disorder, failures:*	
	%		%
70 - 85 I.Q. group	61.9	70 - 85 I.Q. group	72.7
50 - 69 " "	50.0	50 - 69 " "	72.2
40 - 49 " "	50.0	40 - 49 " "	59.3
30 - 39 " "	20.0	30 - 39 " "	nil

All figures in Table IV deal with character disorder present on admission. The heavy incidence of this disorder is apparent, and diminishes abruptly within the low-grade imbecile group. It is accentuated among failures of all groups, excepting this last, where no single case was shown to occur in this survey. It seems likely that this margin of I.Q. (30-39) is where psychotic trends emerge, and play the part we have noted in the failures of this group.

Comparing high-grade and low-grade morons, the incidence of character disorder in failures of both groups is approximately the same. The entire difference in incidence between the two groups (11.6%) is taken up by the higher per-

centage of successes in patients in the high-grade moron group with character disorder on admission. It is apparent that this group is better able to repair its disorder than is the low-grade group. The over-all greater failure incidence among high-grade morons cannot therefore be attributed to the greater incidence of character disorder among them, which is absorbed among the successes, not the failures, of the group.

Indirectly, however, the greater incidence of character disorder in high-grade morons may influence those factors of time and age we have already examined and which we have suggested may be the immediate contributory factor to their relative lack of success. Parents and high schools part with their charges more readily when the element of character disorder is prominent.

We may consider also that persons contributing to the faulty environment which has fostered the more serious degrees of character disorder are not endowed with undue patience or intelligence in their management. This uncongenial background may affect not only character but also intelligence, as has been demonstrated in the work of Skeels and Dye[2] and of Skeels and Harms.[3]

The group of high-grade imbecile successes, with a slightly reduced total incidence, still contains 50% with previous character disorder, which is equal to the incidence among low-grade moron successes. A 12.9% drop in the incidence of character disorder between the failures of these two groups (Table IV) indicates its lessening importance as a contribution to failure in the sub-moronic group.

In the low-grade imbecile group, character disorder has lost all significance as a contributing factor in failure; and this holds good for idiot group discharges also.

DISCUSSION

The prevalence of character disorder among all but the lowest grade of admissions emphasizes the neurotic accompaniment of mental deficiency in its higher grades.

A majority of defectives are markedly suggestible, and display conversion symptoms at some time. Few cases, outside the brain injury and mongol groups, come to us from satisfactory homes with stable parents.

Personality structure has not been assessed in this investigation but might well repay close study, from the point of view of uncovering neurotic patterns of development which militate against the successful habilitation of juvenile mental defectives.

In this province, the mental defective has a definite role in agricultural society, which is of some importance if we bear in mind the population shortage of Canada, and the present drift of young people from the country to industrial centres.

Our understanding of why the mental defective fails in society should not be confined to a knowledge of his I.Q., plus the psychological generalizations currently in vogue. From the medical angle, he must remain an individual case as much as any psychiatric case which has its own all-important facets; it is here we come to understand and treat, rather than to manage, our patients.

CONCLUSION

While most of the points which can be made from this investigation are purely local in effect, certain inferences seem to us capable of general application. These are:

1. The danger of fostering unawareness of their specific limitations amongst high-grade morons trained in the security of an institution.

2. The prime need for treatment of character disorder, which is found to be a common concomitant of juvenile mental deficiency and a main factor in success or failure of borderline and moron groups.

3. The fallacy of assessing mental defectives solely on a basis of I.Q. and specific work performance, without due regard to the personality and character assets of the individual.

4. Benefit of training is possible in all groups, down to and partially including low-grade imbeciles.

5. From these results there appears to be an indication of a definite neurotic/psychotic scale, which forms a background to mental deficiency from the borderline defective group to the idiot category. Further work is necessary to confirm and implement this picture with regard to its possible bearing on etiology and treatment.

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Case Reports

LEVARTERENOL (LEVOPHED) THERAPY IN ACUTE MYOCARDIAL INFARCTION

(INCLUDING CASE REPORT OF RECOVERY FOLLOWING UNUSUALLY HIGH CONCENTRATION)

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LEVARTERENOL (aminoethanol catechol), also known as Levophed, l-nor-adrenaline and l-norepinephrine, was first synthesized in 1904. It is a sympathomimetic primary amine which has been found in blood, urine, adrenal medulla and particularly in phæochromocytoma. There is no longer any doubt that this vasopressor amine has saved the lives of many patients, especially following severe myocardial infarction[3-5] complicated by acute hypotension. The latter is due to the inability of the left heart to maintain an adequate output (cardiogenic shock), and is not rare after an acute myocardial infarction. If not quickly reversed, the condition results in a mortality rate of 80% or higher.[2] Levophed has been shown to combat this condition better than any other therapy, such as retrograde arterial infusions or cortisone administration, and is more effective than any other vasopressor drug.[2] It slows the pulse rate and increases total peripheral resistance by causing generalized vasoconstriction of arteries, capillaries and veins (although it produces coronary vasodilatation[7]). Thus the blood pressure is elevated and the mean aortic pressure rises, producing a proportionate increase of coronary flow with minimal side-effects such as severe arrhythmias. At the same time it produces a decrease in renal plasma flow[6] and a rise in the filtration fraction owing to efferent glomerular arteriolar constriction. It does not produce central nervous system stimulation and tachycardia with the associated anxiety, discomfort and peculiar feelings that follow epinephrine (adrenaline) administration. It is also eight times less toxic. Because of the increase in pulmonary arterial, capillary and venous pressures, the possibility of aggravating or producing pulmonary œdema must be considered, especially in those patients already in congestive heart failure.

The usual response is exemplified in the series of Miller *et al.*[5] Out of nine patients with shock accompanying acute myocardial infarction, five ultimately survived. Without levarterenol no more than two would have recovered. In Kurland and Malach's[3] series of 14 patients there were only four survivals, in spite of the fact that there was a temporary satisfactory pressor response in 12 of 17 courses of treatment. It is noted that in this series the concentration of levarterenol was not increased beyond one ampoule per 1,000 c.c. of infusion (4 micrograms per c.c.). Griffith *et al.*[2] controlled shock in 17 out of 30 patients, using two ampoules of levarterenol per 1,000 c.c. They defined shock as a condition of marked hypotension lasting for an hour or longer, and accompanied by signs of peripheral circulatory collapse. In a patient whose blood pressure had previously been within normal limits, a systolic blood pressure reading of 80 mm. Hg or below was accepted as evidence of shock. A formerly hypertensive patient with a systolic blood pressure of 100 mm. Hg or below was considered to be in shock.

METHOD OF ADMINISTRATION

The levarterenol (Levophed) solutions are prepared by adding 4 c.c. (1 ampoule) levarterenol bitartrate 0.2% (equals 0.1% base) to 1,000 c.c. of 5% dextrose in distilled water, the resultant solution containing 4 mcg. base (8 mcg. bitartrate) per c.c. It has been recommended that if the shock has lasted between one and three hours, showing no response to the usual measures, particularly oxygen and morphine, infusion should begin at 10 drops per minute but should increase to 80 drops per minute if necessary to keep systolic blood pressure over 100 mm. Hg (over 120 if the patient had been hypertensive). In order to limit the total amount of fluid administered, or if blood pressure rise is insufficient, one may according to the recommendations in the literature gradually increase the concentration as much as four times. The highest concentration reported[5] (with recovery) is 100 drops per minute of a solution containing 32 mcg. of levarterenol bitartrate per c.c. (4 ampoules per 1,000 c.c. diluent). The object of this therapy is of course to adjust the rate of flow to

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TABLE I.

SUMMARY OF CASE HISTORY
MRS. M.B., AGED 62 YEARS—ADMITTED JUNE 4, 1955

Date	*Condition of patient*	*Amount of Levophed (per 1,000 c.c. 5% dextrose)*	*Other therapy*	*Other findings*
June 4, 1955	Onset of heart attack, acutely ill.	1 ampoule at 6 to 8 drops per min.	Oxygen, morphine, dicoumarol.	ECG showed extensive cardiac infarct
June 6, 1955	Right and left heart failure; cyanosis, orthopnœa.	As above.	Digitalization, thiomerin, low salt diet.	WBC 14,250 Hb. 84%. Sed. rate 23 mm./hr.
June 8, 1955	Heart failure improving.	4 ampoules at 40 to 60 drops per min.	1,200 calorie diet.	
June 9, 1955	Recurrent hypotension.	5 ampoules at 30 to 60 drops per min.		
June 11, 1955	Recurrent hypotension.	6 ampoules at 40 to 60 drops per min.		
June 15, 1955	Peripheral vascular collapse.	7 ampoules at 50 to 60 drops per min.		
June 18, 1955	Much better.	1 ampoule at 30 drops per min.		
June 23, 1955		1 ampoule at 4 to 8 drops per min.		
June 24, 1955		Discontinued.	2,000 c.c. 5% dextrose in distilled water.	
June 27, 1955	Oxygen no longer necessary.			
July 24, 1955	Out of bed.			Sed. rate and WBC normal.
Aug. 3, 1955	Able to walk length of corridor; discharged.		Dicoumarol stopped.	
April 1956	Able to do her own housework, etc.		Digoxin 0.25 mg. daily, occasional thiomerin.	

hold the blood pressure at the desired level with the minimum rate of administration. The rate of infusion is gradually reduced (and eventually stopped) over a variable period, depending on when the blood pressure maintains itself.

CASE HISTORY* (See Table I)

Mrs. M.B., a 62-year-old white woman, was admitted to the medical ward of the Northwestern General Hospital on June 4, 1955, suffering from severe, squeezing, substernal chest pain which had come on suddenly, lasted three to four hours and was associated with shortness of breath.

Except for the usual reduction in exercise tolerance in a woman of her age and weight, there had been no cardiovascular symptoms nor was there a history of any previous cardiovascular disease or any other significant past illness. There was no diabetes or high blood pressure but she had been overweight for many years.

On admission the patient appeared pale and in distress because of severe chest pain and slight orthopnœa but there was no increased distension of neck veins. Her pulse was feeble and blood pressure 108/80 mm. Hg, with a cardiac rate of 92 per minute and regular. Heart sounds were faint and of poor quality. No significant murmurs or rub were audible. Except for moderate obesity, the remainder of the general physical examination was not remarkable. Her chest was clear, and liver was not palpable or tender. No œdema of ankles or sacrum was present. Ophthalmoscopy revealed slight tortuosity of retinal vessels but no AV nicking or hæmorrhages, exudates or papillœdema. She was immediately placed in an oxygen tent and dicoumarol therapy instituted; morphine sulphate grain ¼ subcutaneously was given three times during the first four hours after admission (to control the pain).

One hour after admission, the patient's blood pressure had fallen to 85/70 mm. Hg while the cardiac rate had risen to 110 per minute. Her pulse became very weak and thready and she appeared to be in extremis. In view of the fact that the blood pressure had remained down for one hour in spite of the above therapy, levarterenol was started. Within a few minutes of beginning the infusion the blood pressure rose to 110/90 mm. Hg and was maintained in that neighbourhood by 1 ampoule* of levarterenol at a rate of 6 to 8 drops per minute.

*Prepared with the assistance of Dr. A. W. Brickenden, Attending Physician, Northwestern General Hospital, Toronto.

*Throughout the history each ampoule refers to 4 c.c. of levarterenol in 1,000 c.c. of 5% intravenous dextrose in distilled water. "Maintenance of blood pressure" means prevention of drop below 100 mm. Hg systolic pressure.

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The clinical diagnosis of an acute myocardial infarction was confirmed by electrocardiograms which showed an extensive anterior cardiac infarction involving the anteroseptal as well as the antero-lateral aspect of the myocardium and with extension through the septum (Fig. 1).

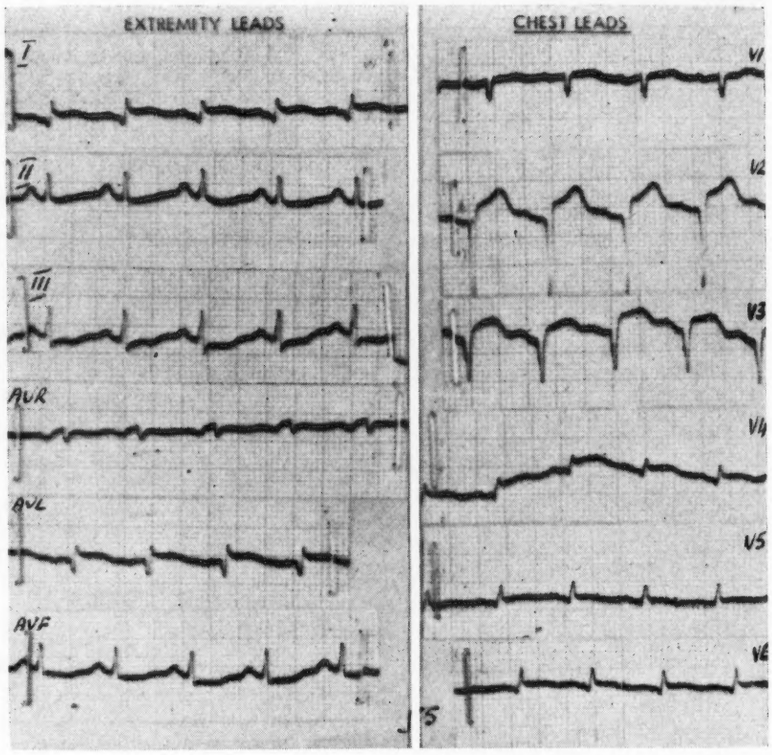

Fig. 1.—Electrocardiograms of Mrs. M.B. June 4.

A chest radiograph taken on June 5 showed clear costophrenic sinuses and a normal-sized heart. Urinalysis showed a trace of protein but was otherwise negative. The white cell count was 14,250, Hb. 84%, sedimentation rate 23 mm. in 1 hour. From the third day onward, the prothrombin time was maintained between 2 and 2½ times the control value by the use of dicoumarol. She was put on a 1,200 calorie diet.

On the third hospital day (June 6), she developed right and left heart failure with fine rales at the chest bases, cyanosis, extreme orthopnœa and œdema of both ankles as well as the sacrum. She was treated with digitalis, mercurial diuretics and low salt diet, which during the following two weeks controlled the failure and produced great symptomatic relief.

Levarterenol therapy had to be continued in varying concentrations for as long as three weeks. From June 4 to June 7, the patient's blood pressure was maintained by 1 ampoule of levarterenol at a rate of 6 to 8 drops per minute. It was noted that she suffered a drop in blood pressure at the slightest movement and that when she was simply turned to be washed, systolic pressure fell as much as 20 to 30 mm. Hg. On June 8, the rate of intravenous infusion with 1 ampoule of levarterenol had to be increased to 60 drops per minute in order to maintain the blood pressure, but in a few hours this failed to produce a systolic blood pressure of more than 80 mm. Hg and the levarterenol was increased to 2 ampoules. When she failed to show an adequate response after increasing the rate of flow to 60 drops per minute, an infusion of 3 ampoules was started. This again failed and she was given 4 ampoules, which at between 40 and 60 drops per minute maintained the blood pressure, until June 9 when it dropped to 60/40 and she went into shock. At that time she was started on a solution containing 5 ampoules of levarterenol, and at a rate of between 30 and 60 drops per minute her blood pressure rose and she improved considerably for several days. On June 11, we were again faced with a drop in blood pressure that did not respond to our maximum infusion rate (60 drops per minute) and the levarterenol was increased to 6 ampoules at a rate of between 40 and 60 drops per minute, at which her blood pressure was maintained. She was continued on the 6 ampoule strength solution until June 15 (except for one six-hour period during which time a seventh ampoule had to be added to the solution. After about 1,000 c.c. of this high concentration we were able to return to the 6 ampoule concentration). Over the next three or four days the strength of the solution was gradually decreased until by June 18 the patient was receiving 1 ampoule at a rate of 30 drops per minute. The drop rate was gradually reduced over the next week until 4 to 8 drops per minute of the 1 ampoule maintained her blood pressure. Several times the drip was stopped, but had to be restarted within a few minutes because of immediate blood pressure drop. It was noteworthy that this very weak concentration made such a great difference. However, by June 24, it could be permanently discontinued. A further 2,000 c.c. of 5% glucose in distilled water was given (in 12 hours) and then intravenous solutions were discontinued.

From the time we were able to stop the levarterenol, the patient made excellent progress. On June 27, she was taken completely out of oxygen. Her blood pressure at that time was 110/80 mm. Hg and her cardiac rate was 88 per minute and regular. There were no longer any signs of right or left heart failure. On July 24 she was allowed up, and ambulation gradually increased from then on. Her white cell count, sedimentation rate and urine were normal at this time, but her chest radiograph showed moderate left ventricular enlargement (with no pulmonary congestion). Although the persistent changes in the RS-T segments in the electrocardiograms (Fig. 2) suggest ventricular aneurysm, this was not confirmed by fluoroscopy. Her dicoumarol was gradually stopped and she was discharged on August 3 feeling well and able to walk the full length of the corridor without discomfort. She was last seen in the outpatient department in April 1956. She is able to do routine housework without discomfort and is living a fairly normal life. She is taking 0.25 mg. of digoxin daily and is on a low salt, low calorie diet.

DISCUSSION

There is no doubt that if 6 (and for a short period 7) ampoules of levarterenol per 1,000 c.c. had not been used, this patient would have died. This disproves the current opinion that if 4 ampoules per 1,000 c.c. does not raise the pressure there is no use in increasing the concentration. The maximum concentration given in this case (56 mcg. of levarterenol bitartrate) is almost twice the highest concentration reported in the literature.[4, 5]

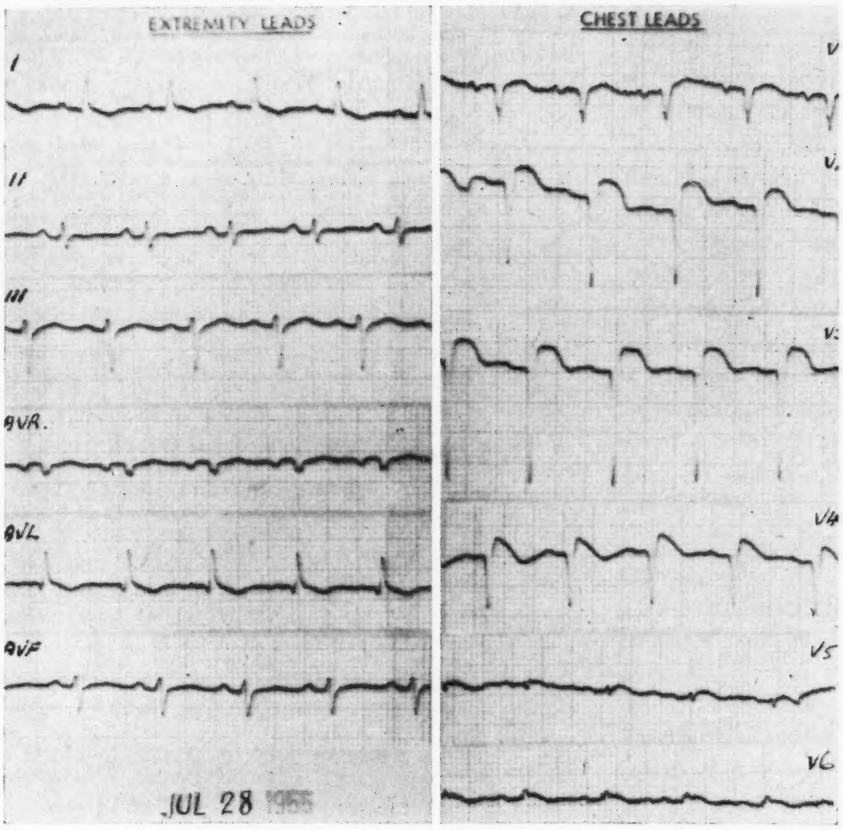

Fig. 2.—Electrocardiograms of Mrs. M.B. July 28.

This most impressive example (together with about 20 other cases of cardiac infarction that have been treated by us with Levophed) allows one to form certain conclusions not too clearly emphasized in the literature.

All agree that the longer the delay in instituting adequate levarterenol therapy, the less the chance of survival.[2] Therefore it is felt that one should not wait for the actual signs of shock, but if the systolic blood pressure remains under 95 mm. Hg (or under 100 in a known hypertensive) in spite of oxygen and morphine (or Demerol) for from one to three hours, this therapy should be started. If clinical evidence of peripheral vascular collapse is present (and not only a drop in blood pressure), it should be started immediately. A good rule is that if more than 60 drops per minute is necessary to maintain the systolic blood pressure as noted above, another ampoule of levarterenol should be added within 5 to 10 minutes. If the desired response is going to be obtained with a certain strength of solution, it is usually instantaneous, and much valuable time is lost if there is further delay before increasing the concentration.

The only satisfactory guide to dosage is the observation of the effect on the patient, and more particularly on the blood pressure. In most patients, 1 ampoule usually suffices, but in the more severe cases the concentration must be increased to 4 times before adequate blood pressure rise is obtained. It should not take more than 20 to 30 minutes to reach this concentration (which if required makes the prognosis worse). However, as this case demonstrates, one may have to give as much as 6 or 7 ampoules per 1,000 c.c., and still get recovery. (We must admit that in about half a dozen other patients given this high concentration there was no effect; in such cases where post-mortem was obtained, very extensive infarctions were found.) One of our patients, A.W., in heart failure and shock secondary to a cardiac infarction, had an excellent blood pressure response with 6 ampoules of levarterenol per 1,000 c.c., but one day later succumbed. Autopsy showed pulmonary congestion as well as a very extensive acute cardiac infarction. If heart failure is present, the drop rate should be reduced by increasing the concentration (e.g. 3 ampoules at the rate of 20 drops per minute rather than 1 ampoule at 60 drops per minute).

All patients on levarterenol therapy should have special nurses constantly present, as blood pressure should be taken every few minutes at first and then every 15 to 20 minutes for as long as this treatment is given. The doctor should explain to them in detail the mechanism and specific purpose of this therapy because, as time goes on, they must constantly increase or decrease the concentration, depending on the blood pressure response. Another need for constant observation is the danger of interstitial escape of levarterenol, which is very painful and may cause necrosis of tissue. Should that occur, the infusion should of course be immediately

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changed to another vein. The best therapy is immediate subcutaneous injection into the involved area of 10 to 20 c.c. distilled water (with 3 to 5 c.c. 2% procaine, which will stop pain immediately), thus diluting the levarterenol. This will usually prevent tissue necrosis, which may be very extensive (within 48 hours or sooner, due to the local vasoconstrictor effect of the drug[1]). To try to avoid this complication, it is wise in all cases where several days or more of therapy are contemplated, to cut down on the vein and insert a small polyethylene tube for a distance of 6 to 8 inches (15-20 cm.) into the vein. In several of our cases where all the peripheral veins were no longer suitable or had collapsed, our surgical confrere was called in to cut down on the femoral vein. In this way the therapy can be continued and the patient given renewed hope. One should emphasize that this latter procedure, although it can be done easily at the bedside, requires special training and should be performed by a qualified surgeon. Although 1 to 6 days is the average length of time the therapy is given, some of our cases, including the above example, required 2 to 3 weeks of therapy. Instead of stopping the intravenous drip as soon as the blood pressure is maintained without the levarterenol, one should immediately start an infusion of 1,000 c.c. of 5% dextrose in distilled water for a further period of 12 to 24 hours in case the pressure drops again (which it commonly does) so that levarterenol can be readministered without delay.

SUMMARY

A case is presented of extensive acute myocardial infarction with secondary shock (peripheral vascular collapse) as well as congestive heart failure. Levarterenol (Levophed) was given as part of the treatment. In order to maintain the blood pressure, the strength of Levophed solution had to be increased to a concentration of 7 ampoules per 1,000 c.c. (56 mcg. of levarterenol bitartrate). This is almost twice the highest concentration (with recovery) reported in the literature. This case demonstrates that stronger solutions of Levophed should be used if necessary and may be life-saving. Some other views on the use of levarterenol therapy are also presented.

The author wishes to take this opportunity to commend the nursing service of the Northwestern General Hospital together with the following staff physicians, who through their diligence and co-operation made the recovery of this patient possible: Drs. H. Kingstone, F. Brereton, W. B. Phair and, particularly, A. W. Brickenden.

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SEVERE STATUS EPILEPTICUS DURING PROLONGED INSULIN COMA*

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APPROXIMATELY one-third of schizophrenic patients undergoing insulin coma therapy experience at least one epileptic seizure in the course of treatment.[1, 2] The percentage of individual shocks in which seizures occur as compared to the total number of shocks is considerably lower. It varies between 2, 5 and 7% in the material of different authors.[3, 4] This is an expression of the fact that patients have usually only one or very few seizures even during long-lasting treatments.

Status epilepticus during insulin coma treatment seems rare. Winkler mentions that he did not see a case of status epilepticus among 330 insulin treated patients, 115 of whom had epileptic seizures during treatment.[3] Von Braunmühl[5] observed 5 instances of "severe status epilepticus" among 566 patients treated with 40,000 insulin shocks; this is a frequency of 0.86% of cases, or 0.0125% of individual treatments. The dangerous nature of this complication, however, becomes clear from the figures given by Kinsey.[6] In his report on the incidence and cause of death in shock therapy, this author states that out of 12,234 insulin treated patients 90 died. Of the 90 deaths, 5 were due to status epilepticus and 38 to hypoglycæmic encephalopathy. Status epilepticus therefore accounts for 5.5% of the deaths, and protracted coma for 42.2%.

On the basis of these figures a status epilepticus during prolonged insulin coma might be

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expected to constitute both a rare and a very dangerous complication. Statistical figures as to its occurrence are not available, however. Detailed reports on pertinent individual cases also seem to be rare. Cloutier[7] reports on a schizophrenic woman who developed a status epilepticus during a prolonged coma and who was treated by bilateral trephination and air insufflation into the cerebral ventricles.

It is the purpose of this report to draw attention to this rare complication, its diagnosis and therapy.

Y.B., aged 20, was admitted to the Allan Memorial Institute on August 15, 1955. He complained of a feeling of nervousness and tension, a peculiar shaking in the back of his head, sleeplessness, and inability to think. He related all this to an incident about two years previously when he was driving in a taxi with a man known to be a homosexual. Since that time he heard voices, referring to him as having homosexual relations with various men. He felt that a gang of homosexuals were after him in order to attack and possibly kill him. Neither occasional heterosexual contacts, nor the "practice of auto-suggestion", nor psychotherapy with a psychiatrist was of any help. He quit his job, withdrew from all outside contacts and "lived in a trance", unable to do anything.

His father had shown frequent violent outbursts of temper which had frightened the patient since early childhood. A younger sister has suffered from epileptic seizures since the age of 5. The patient had between the age of 4 and 8 what were described as "minor seizures". No seizure had occurred since.

Physical examination revealed an essentially healthy young man. Blood pressure 120/80, pulse 80. Neurological and biochemical findings were in the normal range. Fasting blood sugar was 86 mg. %. Blood count and sedimentation rate were normal; Wassermann and Kahn reactions in the serum were negative.

The electroencephalogram (EEG) taken on August 17, 1955, was within normal limits. Background alpha frequency was of low voltage at 10 per sec. There were no significant abnormalities at rest, or with hyperventilation, or in response to photic stimulation. There was no photomyoclonic response. Photic driving was optimal at about 12 per sec. Sedation threshold[8] was 4 mg./kg., which is in the high intermediate range.

A diagnosis of paranoid schizophrenia was made and the patient was started on coma insulin treatment with 20 units of crystalline zinc insulin (CZ insulin). The usual treatment routine was followed. On the second treatment, with an insulin dose of 50 units, the patient developed a grand mal seizure 3½ hours after the injection. Treatment was terminated by intravenous injection of 300 c.c. of 30% glucose. The patient awoke during the injection and remained alert but complained of severe headaches, which persisted through the day. Another grand mal seizure occurred on the fourth treatment, again 3½ hours after the injection of 70 units of CZ insulin. It was again tried to terminate treatment by intravenous glucose but the patient was slow in awakening and the injection had to be repeated. The next three treatments were uneventful. By that time, that is after seven treatments, the patient had gone five times into sopor and twice into coma, and had had 1.05 coma hours.

The eighth treatment was administered on September 2, 1955. One hundred units of CZ insulin were injected intramuscularly at 5:30 a.m., followed according to routine by 0.6 mg. of atropine sulfate subcutaneously and 500 mg. of potassium chloride and 600 mg. of sodium chloride orally. Because of the previous seizures, the patient received in addition 100 mg. of Dilantin and 100 mg. of phenobarbital. At the time of the insulin injection the temperature was 97.1° F., pulse rate 72, respiration 18, blood pressure 128/84.

Treatment progressed normally; patient went into sopor at 8:30 and into coma at 9:45. At 10:15 termination was attempted by gavage with 500 c.c. of 30% glucose.

About 10 minutes later, the respiration rate had increased and the patient vomited with little effort approximately 100 c.c. of fluid. Suction was applied immediately and, as the patient did not show any signs of awakening, 300 c.c. of glucose was administered intravenously, followed at 10:45 by 100 c.c. of 50% glucose. This remained without effect and at 10:55 the patient was pronounced in "prolonged coma" and routine treatment started.*

At 11:05, that is 5 hours 35 min. after the insulin injection and 1 hour 20 min. after onset of coma, the patient became restless, respiration deepened and a grand mal seizure occurred, which lasted for 1½ minutes. It consisted of a tonic phase of about 30 sec. duration and a clonic phase which lasted for about 60 sec. During the seizure the patient bit his tongue and voided. The pupils became maximally dilated and did not react to light; the corneal reflexes were weakly present. There was a deviation of the eyeballs and head to the right. The deep reflexes in the upper and lower limbs were difficult to elicit during the seizure but were found increased afterwards. Babinski and Oppenheim signs could be elicited after the seizure. At this time the pupils were somewhat contracted and reacted sluggishly to light. Consciousness, however, was not regained.

This seizure was followed after a short interval by another of the same pattern and duration, again accompanied by biting of the tongue and lips and followed by pyramidal signs. Grand mal seizures now followed each other at a rate of approximately 2 every 5 minutes. At 11:30, 2 c.c. of Somnifène (Roche) was given intravenously, amounting to 3 grains of allylisopropylbarbituric acid and 3 grains of diethylbarbituric acid. The frequency of the seizures diminished to two about every 10 minutes. Their pattern and duration, however, did not change. Sodium Amytal, 125 mg., was injected intravenously at 11:50 and again at 12:00, followed at 12:15 by 150 mg. of phenobarbital by the intramuscular route.

Eventually, at 12:45, that is 100 minutes after its onset, the status epilepticus subsided. The patient, however, remained unconscious. His temperature had risen to 103° F., the pulse rate was 150, the blood pressure 85/50. The neurological findings were as follows: Pupils medium, react sluggishly to light, eyeballs fixed in midline, corneal reflexes present, deep reflexes increased, pyramidal signs present. The patient did not respond to any kind of stimulation, not even to the most painful, and had to be considered in "deep coma".[9]

At 4:00 p.m. the unconscious patient again became restless. Various involuntary movements including extension spasms were seen at this time, but epileptic seizures did not occur. This restlessness decreased in the late afternoon without any change in the depth of the coma. Some involuntary movements like shaking of the head remained observable until 7:00 next morning.

The blood sugar level showed considerable variations. It was 115 mg. % at 11:45 during the status epilepticus, 150 mg. % at 1:20 when the status was terminated. Although the patient was maintained on the routine treatment, the blood sugar fell to 40 mg. % at 4:00 p.m. when the second period of restlessness started. It went up to 80 mg. % again at 5:00 p.m., when the restlessness decreased, increased to 150 mg. % at 6:45 p.m. and remained at this level until the next day, when it returned to normal.

*The therapeutic measures included the application of amyl nitrite, oxygen, continuous drip of 10% glucose. Nicotinic acid and vitamins B and C were added. High protein milkshakes with potassium chloride and added vitamins were given by gavage in the afternoon.

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Consciousness was regained slowly. At 2:00 a.m. on September 3, the patient responded to painful stimuli; at 7:00 a.m. to verbal stimuli by turning his head. Five hours later he started to speak a few words. For the following two days the patient showed an amnestic syndrome. He was completely disoriented in all three fields, his memory for recent events was severely disturbed, and he had complete amnesia for the events from September 2 until September 5. Confabulations were not elicitable; however, the affect was rather flat and there was no initiative whatever. Neurological findings were normal after September 3.

An EEG record on September 6 showed a background frequency of 9/sec. with irregular slow activity of low voltage most prominently in the right temporal area. On hyperventilation the slow activity was augmented to 4 to 6/sec. There was some driving to photic stimulation but no photomyoclonic response. On September 13, the background alpha activity was about 10½/sec. somewhat irregular. There was still some 4 to 6/sec. low to moderate voltage activity in the temporal areas but considerably less than on September 6. Photic driving was fair.

After September 6, the patient showed considerable and continuous improvement in his mental condition, although insulin treatment was not resumed. Instead, he was for a few days maintained on 100 mg. Dilantin and then on 1 mg. Serpasil t.i.d. He began to mix with other patients and to respond to psychotherapy. He developed insight and repeatedly wanted to know how a relapse could be prevented. He was discharged improved on October 5, 1955.

DISCUSSION

While the diagnosis of prolonged insulin coma rests on the fact that the patient did not show any signs of awakening but remained in deep coma after the application of large amounts (260 g.) of glucose by gavage and the intravenous route, the diagnosis of status epilepticus is based on the typical picture of frequently occurring generalized epileptic seizures between which the patient did not recover consciousness.[10] As the coma was present for a considerable period of time before the first seizure occurred and lasted for many hours after the status was brought under control, it seems safe to assume that we were actually dealing with a status epilepticus which developed during a prolonged insulin coma.

Our patient developed generalized convulsions twice during ordinary insulin shocks, and one severe status epilepticus during a prolonged coma. This seems to indicate a close pathogenic relationship between epileptic seizures and the metabolic changes during insulin shock. It is interesting to note, however, that the blood sugar level was found normal during the status epilepticus but went down to 40 mg. % long after the status had been brought under control. Other factors than the hypoglycæmia *per se* may have been of importance for the pathogenesis of the seizures, among them the patient's constitution (in the widest sense). The fact that approximately one-third of schizophrenic patients undergoing insulin coma treatment develop epileptic seizures, whereas the metabolic changes during insulin shock may be assumed to be similar in the whole group, also seems to indicate a personal pathogenetic factor.

Our patient had had "minor seizures" between the ages of 4 and 8 and his sister is a known epileptic. The patient's electroencephalogram before insulin treatment was found normal. However, Sem-Jacobsen *et al.*[11] found intracerebral paroxysmal dysrhythmias in a number of schizophrenic patients with normal scalp electroencephalograms. Moreover, the figures given by Sem-Jacobsen regarding his schizophrenic patients with paroxysmal intracerebral dysrhythmias coincide fairly well with the percentages of patients who develop seizures during insulin coma treatment.

Treatment of the alarming condition in our patient was empirical but effective. It consisted in the routine treatment of prolonged insulin coma as mentioned above, and in the injection of barbiturates in the relatively high dose of 0.9 g. The latter measure was applied in spite of the fact that the clinical picture before and after the status epilepticus indicated that the insulin-produced depression of brain function had already reached the midbrain level. The beneficial effect of barbiturates on status epilepticus without undue interference with vital functions lends support to Cameron's[12] recommendation that prevention of exhaustion in cases of prolonged insulin coma is of primary importance.

The problem of prevention of prolonged coma will not be discussed here. Whether the status epilepticus could have been prevented is doubtful. Dilantin and phenobarbital, which the patient received after his first seizures had occurred, did not prevent status in the dosage applied. It is interesting to note, however, that the status started after an attack of vomiting, in other words when the parasympathetic system was overactive. A higher dose of atropine than the one the patient usually received with his insulin injection might possibly have been effective as a preventive measure. At any rate, patients with a history of seizures, if only in childhood, or in whose family epilepsy has been noted should be watched most carefully for spontaneous epileptic seizures during insulin coma treatment, even in the absence of a positive EEG record.

SUMMARY

A 20-year-old schizophrenic patient who had had some "minor seizures" during childhood and whose sister was a known epileptic developed convulsive seizures with the second and fourth insulin shock treatments. With the eighth treatment the patient went into prolonged coma during which a severe status epilepticus occurred. The clinical picture is described and the therapy used is discussed.

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RÉSUMÉ

Les auteurs décrivent le cas d'une complication assez rare survenue au cours du traitement classique par coma insulinique. Un jeune homme de 20 ans, souffrant de schizophrénie paranoïde, avait déjà présenté des réactions epileptiques à la suite du second et du quatrième traitement. Après le huitième, le patient demeura en coma prolongé et bientôt entra en "état de mal". Ce patient avait déjà présenté des convulsions isolées, mal décrites, au cours de son enfance. Une sœur est cliniquement reconnue comme épileptique.

Le tableau clinique est présenté, l'attitude thérapeutique est discutée et les suites immédiates sont décrites au cours du travail.

L'examen physique n'avait rien d'anormal. L'examen neurologique en particulier était négatif. Les tests biologiques étaient réguliers: le glucose sanguin à 86 mg. %. L'électroencéphalogramme montrait un rythme alpha de bas voltage à la fréquence de 10/sec., et on ne découvrit pas d'anormalité au cours du sommeil, de l'hyperpnée et de la stroboscopie. Le "seuil de sédation" (Shagass) était de 4 mg./kg., ce qui se situe dans la moyenne élevée.

A cause de ses premières convulsions, le patient recevait 100 mg. de Dilantin et 100 mg. de Phénobarbital avant chaque traitement. Après avoir reçu du glucose par gavage et par voie intraveineuse sans donner signe de réveil, le patient fut prononcé en coma prolongé. Quelques instants plus tard il avait sa première convulsion (période tonique 30 sec., période clonique, 60 sec.), au cours de laquelle il se mordit la langue, et fut incontinent d'urine. Ses pupilles étaient dilatées, mais les reflexes cornéens étaient légèrement présents. On nota également une déviation des yeux et de la tête vers la droite. Après la crise, on pouvait trouver les signes de Babinski et d'Oppenheim. Le patient ne recouvra pas sa conscience. Peu après une autre convulsion de même type suivit et ainsi de suite au rythme de 2 par 5 minutes. A la suite d'administration de Somnifène et d'Amytal, la fréquence diminua à 2 par 10 minutes et au bout d'une heure l'état de mal était vaincu, mais le coma persistait.

Avec les précautions de routine en pareil cas, le patient demeura dans cet état encore 24 htures avant de donner signe de conscience. Pendant les jours suivants il présenta une amnésie des faits récents et une amnésie rétrograde.

Son électroencéphalogramme montra d'abord des ondes lentes dans les régions temporales, puis se regularisa dans les semaines suivantes.

L'état du patient fut amélioré du point de vue symptomatologique à la suite de cet incident et ceci durait encore au moins 6 mois après son congé de l'hôpital.

FATAL DISSEMINATED HISTOPLASMOSIS*

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HISTOPLASMIN SKIN TESTS, conducted by various workers, indicate that subclinical forms of infection with *Histoplasma capsulatum* or immunologically related organisms are not uncommon in Canada. Green[3] found 5.2% positive reactors among 440 veterans at the Deer Lodge Hospital in Winnipeg. According to Heaton,[6] out of 63 students at the University of Toronto with pulmonary calcifications, 36 (57.1%) reacted positively to histoplasmin, 33 (52.4%) to tuberculin and 6 (9.5%) to both. Among 135 first-year medical students at the same university, Heaton and Brown[7] encountered 14 (10.4%) positive histoplasmin reactors. An incidence of about 50% was found by Bowman[1] among his patients in southern Ontario. Guy *et al.*[4] reported 26.7% histoplasmin reactors among 75 school-children in southern Quebec. In the most northern part of Quebec, Guy *et al.*[5] found 4.9% positive reactors among 161 Indians of all ages and 1.5% among 65 Indian children of school age. Stewart,[11] however, failed to find positive histoplasmin reactors among Dalhousie University students who had been life-time residents of the Maritime Provinces and Newfoundland.

Very few clinically suspected or diagnosed cases of infection with *Histoplasma capsulatum* have been reported in this country. Mankiewicz *et al.*[9] reported from Montreal a case of pulmonary histoplasmosis proven by the isolation of *Histoplasma capsulatum* from the sputum. Green[3] mentioned a fatal case encountered in Winnipeg by Lederman.[8] Green reported briefly

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another case from Winnipeg in which the circumstantial evidence favoured the diagnosis of acute pulmonary histoplasmosis. However, he failed to recover the fungus from the patient's sputum. Nuttall-Smith,[10] from Kamloops, B.C., described a case of pulmonary histoplasmosis accompanied by erythema nodosum. However, we agree with Bowman[1] that the evidence in this case was not sufficient for such a diagnosis. Recently, Fish *et al.*[2] reported from Guelph what may have been the first case of canine histoplasmosis in Canada, proven by pathological and mycological studies.

The purpose of this paper is to record a fatal case of disseminated histoplasmosis which was recently encountered in this department. The autopsy was performed at a local hospital and suitable material for cultural studies was not available to us. Nevertheless, we believe that the distribution of the lesions and their histomorphology, together with the presence of typical budding intracellular fungi, provide a sufficient basis for our diagnosis. To our knowledge, this case represents the first instance of histoplasmosis encountered in the Ottawa Valley and possibly the second fatal case in Canada.

B.P., a 13-year-old white girl, was admitted to a local hospital with a history of fever and productive cough of three weeks' duration and amenorrhœa for a period of four months. Physical examination revealed a pale, sickly girl weighing 75 lb. The temperature was 101° F. and the pulse rate 96. There was slight prominence of the eyes and minimal cervical lymphadenopathy. On auscultation, rales and crepitations were heard over the base of the right lung. The urine was unremarkable save for a trace of albumin. The hæmoglobin level was 13.7 g. %, the erythrocyte count 4,500,000 and the leukocyte count 5,150 with 48% neutrophils, 2% eosinophils, 1% basophils, 44% lymphocytes and 5% monocytes. The chest radiograph showed a disseminated micro-nodular infiltration, thought to be compatible with granulomata. A tuberculin patch test was negative and sputum smears and cultures were negative for *Mycobacterium tuberculosis* on several occasions. The patient was treated with polycycline, chloramphenicol, potassium iodate and symptomatic and general supportive measures. During hospitalization, cyanosis, dyspnœa, perspiration and loss of weight were noted. The condition remained static for two consecutive weeks, after which the patient showed gradual improvement manifested by disappearance of dyspnœa, cyanosis and perspiration, and improvement of appetite. The chest radiograph also showed a gradual clearing of the infiltration in the upper lobes of both lungs. However, the temperature remained elevated and oscillated between 98 and 103° F. The patient was discharged about four weeks after admission with the diagnoses of "mycosis and bronchopneumonia."

During the next three weeks she continued to have fever, cough and loss of weight and developed dysphagia. On the fourth week she was readmitted to the same hospital in a moribund state.

Physical examination at that time revealed dyspnœa, emaciation, dehydration, swelling and reddening of the pharynx, œdema of the uvula and mild hepatosplenomegaly. The urine contained albumin in quantities estimated to be from a trace to 2 plus, a few granular casts and a few leukocytes. The hæmoglobin level was 7.9 g. %, the erythrocyte count 2,200,000 and the leukocyte count from 1700 to 2000 with 65 to 73% neutrophils, 0 to 1% eosinophils, 26 to 34% lymphocytes and 0 to 3% monocytes. The chest radiograph showed mild accentuation of the bronchovascular markings at both bases. Clinical diagnoses of leukæmia, lupus erythematosus and Gaucher's disease were entertained at this time. The patient was given a variety of antibiotics, blood transfusions and general supportive treatment but her condition rapidly deteriorated. She developed intermittent periods of somnolence and agitation and generalized purpura with bleeding from the nose, lips and mouth, hæmoptysis, hæmatemesis and melæna. On the fourth day in hospital she lapsed into coma, and died on the following day.

Fig. 1.—Fatal disseminated histoplasmosis. Section of adrenal showing an area of necrosis surrounded by histiocytes containing *Histoplasma capsulatum*. The colour of the cytoplasm of these cells varies from pale grey to almost black and depends on the number of fungi. Many Histoplasma-laden histiocytes are also seen in the cortex elsewhere. P.A.S. × 70.

Autopsy (E.S.-176-56)—Gross findings: As stated above, the autopsy was performed elsewhere and blocks of tissue were sent to this laboratory for histological examination. Data concerning the appearance of the organs were incomplete and were compiled partly from the autopsy notes and partly from the examination of formalin-fixed tissue blocks.

The body was estimated to weigh 65 lb. The lungs weighed together 510 g. and showed œdema and patchy hæmorrhages. The liver weighed 1800 g., was firm, and its cut surfaces displayed a nutmeg pattern. The spleen weighed 350 g. and was red and firm. The adrenal glands were not weighed but were thought to be enlarged. They showed patchy and confluent areas of necrosis involving the cortex and medulla bilaterally and their capsules were covered by adherent, indurated fatty tissue. The kidneys weighed 130 and 150 g. Both organs were pale and on section revealed areas of creamy discoloration, not exceeding 0.5 cm. in diameter, in the renal pyramids. There was slight generalized lymph node enlargement and one of the abdominal lymph nodes showed extensive necrosis. The other thoracic and abdominal organs were stated to have been unremarkable. The brain and spinal cord were not examined.

Microscopic findings: Lungs—Sections showed diffuse interstitial pneumonia, foci of acute bacterial bronchopneumonia and patchy hæmorrhages. The alveolar septa contained a mixed cellular inflammatory exudate composed of lymphocytes, histiocytes, a few polymorphonuclear leukocytes and a few scattered multinucleated giant cells. The histiocytes occasionally formed small granulomas but predominantly were scattered in the alveolar septa and the alveoli. Caseous necrosis was not

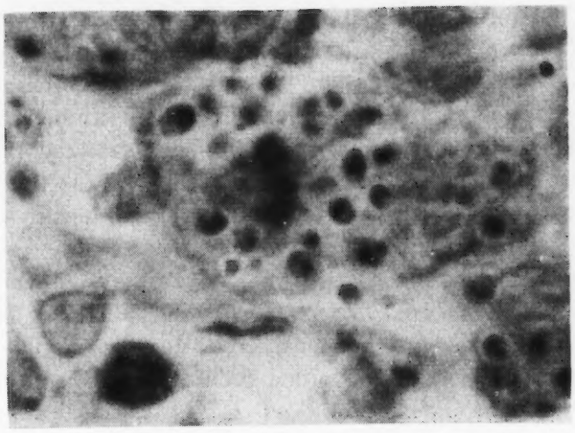

Fig. 2.—Fatal disseminated histoplasmosis. Section of bone marrow showing a histiocyte in mitosis. The cell contains numerous yeast forms of *Histoplasma capsulatum* several of which show evidence of budding. Giemsa × 1200.

seen. Sections stained by the P.A.S. (periodic acid-Schiff) procedure showed that a few histiocytes contained the yeast form of *Histoplasma capsulatum*. Liver—There was severe chronic passive congestion and marked fatty metamorphosis. Sections stained by the P.A.S. procedure showed numerous yeast forms of *Histoplasma capsulatum* within many reticulo-endothelial cells lining the liver sinusoids. Occasionally, these cells formed small groups. Caseation necrosis was not seen. Spleen—Sections showed numerous diffusely scattered histiocytic granulomas and single histiocytic cells. Some of the granulomatous lesions showed evidence of necrosis. Intracellular *Histoplasma capsulatum* was observed in both the H.P.S. (hæmalum-phloxine-saffron) and P.A.S. stained preparations. Lymph nodes—One of the lymph nodes showed marked depletion of lymphoid follicles and marked dilatation of the entire sinusoidal net. The latter contained numerous desquamated reticulo-endothelial cells, lymphocytes, erythrocytes, a few polymorphonuclear leukocytes, a few megakaryocytes and an occasional multinucleated giant cell. *Histoplasma capsulatum* was observed within some of the reticulo-endothelial cells in the P.A.S. stained preparations only. Another lymph node was completely replaced by caseous necrotic material. This was surrounded by a moderate number of Histoplasma-laden histiocytes and a wide band of dense fibrous tissue. Adrenal glands—Sections showed extensive patchy and confluent areas of necrosis involving the medulla and cortex of both glands. The necrotic areas were surrounded by innumerable histiocytes which were also present singly and in small groups elsewhere in the parenchyma of both glands (Fig. 1) and in the periadrenal fibro-fatty tissue. The yeast forms of the fungus within these histiocytes were demonstrated in both the H.P.S. and P.A.S. preparations. Kidneys—The renal pyramids and papillæ showed numerous scattered groups of Histoplasma-laden histiocytes associated with areas of necrosis in the intertubular interstitium and disruption of the continuity of the tubular walls. The renal cortices showed no lesions. Bone marrow—The hæmopoietic tissue showed extensive replacement by numerous Histoplasma-laden histiocytes. These were scattered either singly or in groups throughout the entire section and some of them showed mitotic activity (Fig. 2). The histoplasma displayed many budding forms. Thyroid, heart, pancreas and internal genital organs were unremarkable.

SUMMARY

A fatal case of disseminated histoplasmosis is presented in which the diagnosis was made on the microscopic examination of autopsy material. The Canadian literature on the subject is reviewed briefly.

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CLINICAL REPORT ON Q FEVER*

FIRST CASE IN CANADA

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IN 1937, E. H. DERRICK, after a two-year survey in Queensland meat plants, described a new febrile syndrome which he then called Q fever.[1] "Q" was for "query", thereby meaning that he was dealing with a still unclassified disease; the condition has since then often been misnamed "Queensland fever".[2] A few months later, laboratory data showed that the etiological agent was a rickettsia (*Rickettsia burneti*), but on account of particular experimental and clinical features it was eventually classified in a new species, *Coxiella burneti*.[3]

Since then, cases of Q fever have been identified in nearly every country of the world. As early as 1939, R. E. Dyer isolated the Nine Mile strain in Montana and proved its identity with the Australian type.[4] The first case diagnosed in the Eastern States was mentioned in 1949.[5] In Canada, Pavilanis and his associates have investigated asymptomatic persons in Quebec and found the existence of positive serological reactions,[6] but it seems that no clinical report relating to Q fever has yet been published. We presume that this one is the first.

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P.A.L., aged 22, a farmer living in the Eastern Townships (Que.), was referred to us on July 31, 1955, for pulmonary investigation. He informed us that four months previously, after a few days of grippal malaise, he rapidly developed shortness of breath on exertion and had a morning cough raising a very viscous mucopurulent sputum, some fever, as high as 104° F., and a non-localized headache of moderate intensity. On the first day of admission, he complained of a marked asthenia, anorexia, and of a dull pain localized under the right scapula, exacerbated by coughing and by deep inspiration. He also noted a loss of 30 lb. weight since the beginning of his illness, and tinnitus for the last seven days. A blood culture at a peak of fever had been negative. Before his admission, the patient had received high dosage of antibiotics and anti-brucellosis therapy.

On physical examination, the man appeared normal, with weight and height 143 lb. and 5'8". The temperature was 98° F. The pharyngeal mucosa was red and the throat showed some whitish aerated secretions; a few small and non-tender lymph nodes were palpable in the anterior cervical chains. The heart sounds were feeble at 76 per min., and the blood pressure was 110/70 mm. Hg. There was no abnormal dullness in the chest, and moist rales were audible in the lower third of both lungs. Apart from these features, clinical examination was entirely negative, except for a scar of a right inguinal herniorraphy.

The urine was normal, the white cell count 12,600 with 83% neutrophils; the sedimentation rate was 5 mm. in one hour (Cutler), the V.D.R.L. negative, and a pulmonary radiograph revealed a pronounced linear marking in the middle third of the right lung.

Sputum contained no acid-fast elements (six direct examinations and six cultures), no pathogenic bacteria or fungi. The following serological tests were found negative: Paul-Bunnell typhoid, paratyphoid A and B and brucellosis. Skin tests with "Brucellergen", blastomycin, histoplasmin and coccidioidomycin were also negative. Ova of parasites could not be found in fæces, and a culture of urine grew coagulase-negative *Staphylococcus albus*. The maximal breathing capacity and the pulmonary volume were within normal limits. A biopsy of a cervical lymph node showed regressive signs of a subacute non-specific inflammation.

We then requested the services of the Institute of Microbiology, University of Montreal, for serological diagnosis of viral and rickettsial diseases; the complement fixation test with Q fever antigen was found strongly positive at 1 in 4 titre and slightly positive at 1 in 8 titre in two specimens of serum taken on August 19 and 25, 1955.

The patient was discharged from hospital on September 3; though he had not been given any anti-infective therapy, he had gained 12 lb. in weight and was feeling much improved. He came back five days later because his temperature had risen to 103° F. for the last three days. Within 24 hours the fever disappeared; the previous sero-diagnostic test was repeated on September 12 and was positive at 1 in 16. When seen again on October 11, the titre had risen to 1 in 32 and it returned to 1 in 4 a month later.

DISCUSSION

The causative agent of Q fever is morphologically identical with the virus of psittacosis (rod or coccoid forms). It is considered as the most resistant of non-sporulated elements and can be cultivated in chicken embryos. *Coxiella burneti* has been isolated from blood, urine, fæces and sputum of infected humans; it does not give either Weil-Felix or cold agglutinin reactions. The infection can be demonstrated by isolating *C. burneti* itself after injection into guinea-pigs, but serological methods are usually used; these include complement fixation, microscopic or macroscopic agglutination, and neutralization. These reactions are highly specific, the second becoming positive later but remaining positive longer.[7] Complement fixing antibodies are detectable from the 7th to the 13th day of illness and may persist for many months. A titre of 1 in 16 or higher is considered significant, particularly if there is some increment on repetition of the test.[8]

The severity of the illness is related to the titre of antibodies and to the duration of their presence in serum.[9] Our patient's serum had the following titres in this order: 1 in 4, 1 in 8, 1 in 16, 1 in 32, 1 in 4. The mode of transmission of Q fever seems today thoroughly elucidated. Rodents are considered to be a natural source of infection; ticks carry the infection to mammals, especially cattle, the fæces of which contaminate soil and dust-laden air. A human infestation may arise from any one of these stages, but there is no direct transfer from ticks to humans, and transmission of the infection from man to man is exceptional.[10, 11] Raw milk ingestion is the principal route of human infection in regions where the disease is endemic. The digestive, respiratory, conjunctival and percutaneous routes of introduction are generally accepted.

Though we do not know anything about the cattle of the district inhabited by our patient, we can state three facts: he did not travel out of the country, he drank raw milk, and he had visited exotic animals in a local zoo more than once.

Very few post-mortem examinations have permitted the study of pathological lesions produced by Q fever in man. More often, lobar or segmental consolidations in the lungs have been encountered, with serofibrinous exudation within the bronchial tree. Splenic enlargement and cerebral and testicular lesions have also been described.

The disease is naturally more often found in individuals more exposed to infection, such as workers in meat or dairy plants or laboratories, cattlemen and veterinarians. The incubation period is usually said to vary from 12 to 26 days. It may be shorter or longer, as recently

demonstrated by Tigertt and Benenson;[12] moreover, these authors have proved that the time elapsing from infection to manifestation of the disease in man is in close relation to the infecting dose of *C. burneti.*

Clinical manifestations can be divided into two groups. First, there are the symptoms common to every febrile illness and not of particular interest; however, most authors insist upon the abruptness of onset and the retro-orbital location of the headache. Second, the absence of a characteristic rash and the presence of pneumonic manifestations are both said to be differential signs from other rickettsioses. Nearly 90% of patients present pulmonary involvement detectable on roentgen examination and often identical with a picture of pneumococcus pneumonia. The hilar surcharge and the vascular engorgement so often seen in atypical pneumonia are usually absent. Resolution becomes apparent as soon as the temperature is back to normal.[13]

The disease usually continues for two to four weeks, but it is not infrequent to observe longer attacks; recurring forms of many months' duration have been reported.[9] In retrospect, we judge that the clinical picture in our case was in accordance with the descriptions given in many papers on this subject.

One should suspect Q fever when dealing with a fever of obscure etiology, especially if, for some reason, the patient is susceptible. The disease should also be considered in differential diagnosis of brucellosis, influenza, typhoid, tularæmia, psittacosis and atypical pneumonia.[14] Laboratory data that confirm the presence of the disease are obtainable from serological tests, as mentioned before. For completeness, we may note the availability of a specific skin test for detection of recent or remote infection with *C. burneti*; a positive reaction should be detectable from the third to eighth day of illness and should persist for four to five years and even throughout life.[15] Q fever produces prolonged immunity.

There is no specific treatment or method of human immunization. However, Huebner[16] has reported some more than satisfactory results after injection of a dead vaccine into dairy cattle. According to experienced authors, aureomycin is the drug of choice. The most recent report available on this subject is that of Meiklejohn and his associates,[17] who observed a favourable response to the drug in 71% of their 45 cases. Chloramphenicol and terramycin have been of some value, while streptomycin and penicillin were ineffective.

SUMMARY

A case of Q fever is presented.

This is thought to be the first clinical report on the subject in Canada.

A brief study of the disease accompanies this presentation.

We wish to express our sincere gratitude to Dr. Somlo of the Institute of Microbiology of the University of Montreal for his co-operation and to Dr. Gagnon of Granby who kindly referred the case to us.

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SEX CHROMATIN IN ORAL SMEARS

Dixon and Torr *(Brit. M. J.*, 2: 799, 1956) report that the examination of oral smears from 260 subjects, varying widely in age and race, enabled the chromosomal sex to be determined with considerable accuracy. With increasing experience in assessment the diagnosis becomes progressively more accurate. The procedure is simple in its application and, if necessary, may be readily repeated.

The findings of previous workers have been confirmed and a number of criteria established, the use of which may help to standardize the method and ensure correct diagnosis.

Determinations of the percentage of cells in the amniotic fluid that are suitable for the sex diagnosis gave, for the cases in the sixth, seventh and ninth months, a mean of 12% suitable cells both for males and for females. In the one case in the third month 60% of the cells were suitable for the diagnosis.

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Clinical and Laboratory Notes

CLINICAL STUDIES WITH POWDERED SOBEE, A NEW MILK SUBSTITUTE*

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A NEW SOYBEAN PRODUCT, Powdered Sobee,† has been studied and found to be acceptable as a milk substitute in the feeding of allergic infants. The composition of this product is shown in Table I. When prepared in the usual proportion of 1 level measure to 2 fluid ounces of water, the resulting formula supplies 19% of its calories from protein, 35% from fat and 46% from carbohydrate. Each fluid ounce of this formula supplies 20 calories. Nursing bottles containing this product may be autoclaved without difficulty.

TABLE I.

APPROXIMATE COMPOSITION OF POWDERED SOBEE

	Powder	*Normal dilution**
	%	%
Protein	22.4	3.4
Fat	17.9	2.7
Carbohydrate	53.1	8.1
Fibre	1.0	0.2
Ash	3.4	0.5
Moisture	2.2	85.1

*1 level measure to 2 fluid ounces of water.

METHOD OF STUDY

Powdered Sobee has now been tested as a milk substitute in 25 infants varying in age from 1 week to 23 months. The average age of the patients was 7½ months. Of these 25 infants, 8 had proven gastrointestinal allergy including allergy to cow's milk, 7 infantile eczema, 5 possible but not proven gastrointestinal allergy, 3 asthma, and 2 miscellaneous conditions. In most cases, the formula was fed using a dilution of 1 level measure of the powder to 2 ounces of water. In 4 cases, because of the early age of the infant or because all other foods had been poorly tolerated, a weaker dilution was used. In these cases the proportion used initially was 1 level measure of Powdered Sobee to 4 ounces of water.

RESULTS

The Sobee formula was taken well by 23 of the 25 infants in the study. One infant took it only if it was mixed with the cereal, and one refused to take it at all. There were 15 outpatients and 10 inpatients. Fourteen of the outpatients accepted the formula readily and received it for an average of two months (range ¼ to 5 months). The 10 inpatients received the material for an average of ½ month (range ¼ to 2 months). The shorter period of observation in these patients was due to their discharge from the hospital.

Weight gain was satisfactory in all cases during the periods of observation. For the most part stools were of normal colour and were soft in consistency. This is in contradistinction to the very loose stools that resulted when many of the patients received cow's milk. The number of stools was usually 1 to 4 daily, which is in the normal range for infants of this age. Two patients showed a reduction in number of stools when changed from cow's milk, but did have up to 7 to 10 stools daily. No untoward symptoms were observed in the patients of this series.

CONCLUSIONS

From the data presented, it is evident that Powdered Sobee is a satisfactory milk substitute for infants who cannot tolerate cow's milk. Infants who were fed Powdered Sobee showed normal growth and had satisfactory stools. In general, infants accepted the formula very well.

*From the Allergy Clinic, Hospital for Sick Children, Toronto; and the Department of Pædiatrics, University of Toronto.

†Supplied by Mead Johnson & Company of Canada, Limited.

EXTRACELLULAR FLUID VOLUME IN HYPERTENSION*

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METHODS USED for the determination of extracellular fluid volumes are dependent upon vascular permeability. We have shown that in the disease termed essential hypertension there is diminished vascular permeability, which is perhaps the salient feature of this disease.[1] Our method (*vide infra*) for the determination of extracellular fluid volume can be varied to take into account this permeability change. We are reporting the extracellular fluid volume determinations which we have carried out in our studies on patients with essential hypertension.

*This research was done on the Second (Cornell) Surgical Division of Bellevue Hospital, New York, N.Y., U.S.A.

TABLE I.

Patient	*Sex*	*Age*	*Type*	*Diagnosis*	*Blood pressure*	*Weight (Kg.)*	*Fat Wgt. (Kg.)*	*LMM (Kg.)*	*ECF*	*%LMM*	*%Wgt.*
L.P.	M	45	IIIss	Hypertension sympathectomized	Pre-op. 270/130, Post-op. 134/76	56.6	8.6	48	11900	24.8	20.9
W.A.	M	41	II	Hypertension 3+ retinopathy	235/160	67.3	4.5	52.8	12050	19.2	17.9
R.L.	M	54	IIIss	Hypertensive	210/190	63.6	7.8	55.8	14700	26.4	23.5
K.H.	F	65	IVss	Carcinoma of breast, cardio-vascular disease	260/120 200/120	56.9	11.9	45	13250	29.4	23.3
J.W.	F	53	IIss	Pelvic fracture, essential hyperten.	260/120	49.6	4.7	44.9	10130	22.6	20.5
F.U.	F	40	V	Hypertensive with borderline failure	255/135	70	16.8	53.2	12300	23.1	17.6
P.P.	M	63	IIIss	Varicose veins fibrillation	190/110	61.2	9.3	51.9	10800	20.8	17.6
F.M.	M	47	IIIss	Varicose veins cardiac hypertrophy	130/88 170/110 220/125	66.5	10.1	56.4	9050	16.1	13.6
S.F.	M	62	Vss	Chronic glomerular nephritis	160/110	86.2	23.3	62.9	15800	25.1	18.3
T.P.	M	72	VI	Osteoarthritis, cardio-renal failure	190/76 260/140	75	22.5	52.5	12180	23.2	16.2
E.D.	M	69	I	Uræmia, benign prostatic hyper-tension, dead	130/70	58	.63	57.4	10300	18.0	17.8

METHOD

The method for the determination of extracellular fluid volume, reported in full elsewhere,[2] briefly consists of the following:

Blank blood and urine samples are drawn in the morning from a fasting subject. One thousand mg. of inulin is given intravenously and 70 minutes later the urine secreted is collected and the blood sample is drawn. The amount of insulin remaining in the body at this moment is divided by the plasma inulin concentration in mg. %. This gives the extracellular fluid volume.

RESULTS

Table I presents the details of this study. Therein "Type" refers to the endomorph rating of the subject's somatotype.[3] "% LMM" indicates the volume of extracellular fluid per kg. of lean muscle mass, and "% Wgt." refers to the volume of extracellular fluid per kg. of total body weight.

We found the extracellular fluid volume in essential hypertension to be 18.8% of total body weight, or 22.6% of lean muscle mass for adults of both sexes. The extracellular fluid volume in normal adult males is 19.2% of total body weight, or 22.9% of lean muscle mass, and in females is 18.2% of total body weight, or 22.0% of lean muscle mass.[4]

SUMMARY

In studying the extracellular fluid volume by our own method, in normal subjects and in subjects with essential hypertension, we did not find any significant difference.

The extracellular fluid volume in essential hypertension is 18.8% of total body weight or 22.6% of lean muscle mass. The extracellular fluid volume in normal adults of both sexes is 18.7% of total body weight or 22.5% of lean muscle mass.

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PITFALLS IN MEDICINE

To prove the doctor wrong is a favourite sport, though few would go as far as the gentleman in Sam Weller's story, who, warned against eating muffins by his physician, promptly consumed a large quantity of them and then blew his brains out just to show that muffins were wholesome and harmless.

In his Croonian lectures delivered at the Royal College of Physicians, London, this year, Dr. Douthwaite of Guy's Hospital gives many examples of the way in which the cards may be stacked against the physician both in diagnosis and prognosis. His lectures (*Brit. M. J.*, 2: 895 and 958, 1956) deal with diagnostic mistakes encountered over a period of 25 years, and he notes the relative ease with which the errors of others can be recalled while one's own shortcomings are lost to memory unless recorded on paper. Dr. Douthwaite suggests that in diagnostic failure the cause is apt to lie with the physician or surgeon rather than with the patient or the obscurity of the disease. Nevertheless, some of the examples he cites would have been a formidable challenge to the giants of medicine.

Dr. Douthwaite deplores the decline in visual appraisal. "It is a poor physician," he says, "who cannot at a glance detect, or at least suspect, advanced cirrhosis of the liver, mitral stenosis, or emphysema, and who will not recognize hysteria from the smile of Christian resignation in a welter of agonizing symptoms." He also suggests that the limit of usefulness of inspection has not been reached, citing koilonychia and squatting as two findings whose significance has only recently been understood. Moreover, simple things may be overlooked; an elderly man with persistent vomiting after digitalis may have a strangulated hernia; a drowsy woman with hæmatemesis may be suffering from uræmia, obvious to a physician with a good sense of smell.

Dr. Douthwaite has some bitter things to say about the science of radiology. He notes that the practice of regarding the radiologist's report as infallible often leads to error; the more experienced the radiologist, the more cautious he will be in stating his findings. It is the radiodiagnostician with a poor grounding in medicine and surgery who is most prone to give a dogmatic and detailed diagnosis, and the radiological ignorance of the British general practitioner (now kept out of the x-ray room by the bumbledom of the National Health Service) does nothing to help.

"There is an area of radiological romance which is bounded above by the pylorus and below by the ileocæcal valve. This stretch of gut, as yet inaccessible to even the most determined endoscopist, provides material for the doubtful claims of duodenitis, jejunitis and ileitis. Once these labels have been accepted by patient and doctor the incentive to search for a rational explanation of symptoms wanes and leads to treatment for a condition which seldom exists." The moral is that specialization without extensive knowledge of general medical and surgical diagnosis endangers efficiency.

Once again the truth is hammered home that accurate and unhurried history taking is an essential to good diagnosis. In evaluation of the history, the physician should try to commit himself to a firm opinion. The aim of the procedure is to make a *diagnosis*, not an all-embracing *differential diagnosis*. In hospital work, this diagnosis should be communicated to one's colleagues and students, so that it may be recorded. Hence of course the intellectual value of the clinico-pathological conference. Dr. Douthwaite suggests that a useful exercise is to attempt the diagnosis from the history and inspection alone. The results will often show how little the many auxiliary tests are really needed.

We have all encountered the pests that Dr. Douthwaite describes—the voluble relations who by the misinformation they volunteer end in muddling both the patient and doctor. He also mentions that odd social phenomenon, the highly educated idiot (the hero of the British movie *Private's Progress* is an excellent example). He

stresses the danger of fatigue and of slipping imperceptibly into rigid habits of thought. "Just as thirty years ago the advance of medicine was arrested by the theory of focal sepsis, so today the search for truth may be imperilled by the parrot-cries of "adaptation reactions" and "collagen diseases". It is easy to slip into unhelpful pseudo-diagnosis such as 'cerebral catastrophe' or 'acute abdomen', or the latest futility, 'cardiac episode'."

The danger of making a diagnosis of mental illness in such cases as hidden carcinoma (pain in the back due to metastases from a pancreatic or prostatic tumour may be unassociated with positive x-ray findings for months or even years) is ever present; even the chronic neurotic can develop organic disease. The drug-induced diseases must also be kept in mind. Lassitude, low blood pressure, low blood sugar and a lag curve in the glucose tolerance test may all be due to barbiturate medication.

Among the pitfalls due to unusual disease patterns of common disease, Dr. Douthwaite mentions the bizarre manifestations of coronary disease (typical pain without ECG findings; simulation of coronary disease by gallbladder lesion), and remarks that the appendix is responsible for more strange abdominal symptoms than any other organ. Diarrhœa due to simple intestinal hurry in a chronically tense and anxious individual appears to be commoner in recent years.

After studying these lectures, one is left in complete agreement with Dr. Douthwaite when he says:

"When we think of the multitude of impediments to our smooth passage along the road to diagnosis it may make us wonder at times that we are so often right. The patient's mental ability, his level of intelligence, his attitude towards his symptoms, his fear of disease, his inability to express himself clearly, the different meanings which people apply to the same word, the jumble of symptoms mixed up with irrelevancies, all produce a mountainous hazard to success. This is increased yet further by the vagaries of disease, often shown in most misleading guises, seldom reproducing itself faithfully in one patient after another, and liable to throw out symptoms and signs like sports in evolution."

Failure on the part of the legal profession and the general public to realize that diagnosis in medicine is infinitely more complex than diagnosis in a machine-repair shop, and that the unfortunate general practitioner has to have a greater overall efficiency than the specialist, has led to much grossly unfair recrimination and litigation. Unfortunately, in this technological age, this state of affairs is likely to continue.

Editorial Comments

LE MÉTABÔLISME CELLULAIRE: APERÇUS EXPÉRIMENTALES ET THÉRAPEUTIQUES

Dans une étude paru dans *La Presse Médicale,* Laborit et Huguenard dressent le bilan d'une étude expérimentale de la cellule et sa membrane structure polarisée à travers laquelle s'effectuent ses échanges.

Les variations de la teneur ionique du sérum et des excréta permettent de prendre une connaissance approximative du fonctionnement cellulaire suivant certaines lois générales mises en évidence sur l'organe isolé, mais qui paraissent conserver une certaine valeur sur l'organisme entier.

Dans la fibre musculaire l'actine et la myosine peuvent être à l'état associé ou dissocié. L'association, qui nécessite la présence d'A.T.P., provoque l'augmentation du tonus et la contraction musculaire. Elle est liée à la richesse ionique intracellulaire, en ions K—en particulier, donc à la valeur du potentiel de membrane. Toute diminution de l'un ou de l'autre de ces facteurs favorise l'association de l'actine et de la myosine, en actomyosine, augmente donc le tonus, et inversement. Ces faits ont été mis en évidence sur l'organe isolé.

Laborit et Huguenard ont tenté l'application de ces notions au système cardiovasculaire et pensent qu'elles sont valables dans une certaine mesure pour l'organisme entier.

Parmi les agents polarisants, les sympatholytiques, comme Houssay et Gershmann l'ont montré, provoquent une hypokaliémie qui paraît en rapport avec une augmentation de potassium intracellulaire. Il en est de même des ganglioplégiques et des neuroplégiques. L'association insuline—glucose a le même effet. Ces substances diminuent le tonus cardiaque et vasculaire. L'hyperventilation qui diminue la teneur en ions H extracellulaires fait de même.

Les agents dépolarisants: adrénaline, noradrénaline, excitation sympathique (réalisée par l'occlusion bicarotidienne, l'excitation du bout central du vague, l'injection d'acétylcholine sur l'animal atropinisé) augmentent la kaliémie au dépens du potassium intracellulaire.

Toute agression s'accompagne d'une réaction organique. Or les éléments de cette réaction, adrénaline, noradrénaline, hormones corticosurrénaliennes, aboutissent à un catabolisme

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décompensé avec acidose. Dépolarisation membranaire, rétention sodée intracellulaire, fuite potassique extracellulaire en seront la conséquence.

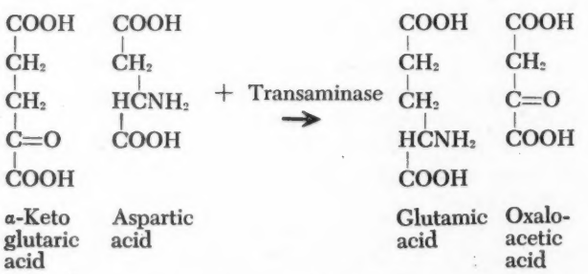
La saignée brutale dépolarise; lente et suivie de dilution, elle polarise. En outre, l'augmentation de Na extra-cellulaire favorise la dépolarisation. De même l'hypothermie.

Un métabolisme cellulaire efficace est fonction d'une polarisation correcte. Pour maintenir celle-ci il faut pouvoir contrôler en particulier les mouvements de K et Na.

La réanimation générale doit s'exercer des deux côtés de la membrane cellulaire et craindre l'augmentation de la concentration en Na extracellulaire. Ces notions ont des conséquences importantes pour la ressuscitation cardiaque; en anesthésie; dans les traitements du choc (neuroplégiques, insuline-glucose, hyperventilation), de l'hypertension, de l'éclampsie, des affections cardiaques. La saignée doit être revue sous cet angle. Conduite parallèlement à une perfusion asodée, de composition ionique déterminée, conjugée au glucose et insuline, elle peut favoriser une diminution du tonus cardiovasculaire et de trouver d'autres indications thérapeutiques que l'œdème aigu du poumon.

GLUTAMIC OXALOACETIC TRANSAMINASE ACTIVITY IN SERUM

One of the most interesting recent adaptations of biochemistry to the study of disease concerns the enzymes of tissue metabolism. Such a specific enzyme is glutamic oxaloacetic transaminase (GO-T). It is concerned with the exchange of the α-amino group of aspartic acid and the α-keto group of α-ketoglutaric acid to form a new compound glutamic acid and a new α-keto acid, oxaloacetic acid.



Cohen and Hekhuis[1, 2] and Green *et al.*[3] described GO-T concentration and distribution in various tissues. Heart muscle was found to harbour greatest activity of this enzyme, followed in decreasing order by skeletal muscle, brain, liver, and kidney. LaDue and his coworkers at the Sloan-Kettering Institute in New York studied the transaminase activity of serum (SGO-T).[4-7]

Transaminase activity was demonstrated on the substrate in serum[8] and may be measured by paper chromatography,[9] spectrophotometrically,[9, 10] and colorimetrically[11]; it is measured in arbitrary units. The normal range for human serum is 15-30 units while heart muscle has about 10,000 times this activity.[12]

When myocardial infarction develops, the injured heart muscle loses enzyme to the serum. Similarly increased SGO-T activity will result from injury to the heart and skeletal muscle, liver, and possibly kidney, from any damage of an ischæmic, infectious, toxic or traumatic nature. The curve of several determinations of SGO-T activity following both experimental infarction in dogs and myocardial infarction in patients[13] shows a rapid rise to a maximum level at the end of 24-36 hours followed by a fall to normal in 2-5 days. The extent of the rise is said to be roughly proportional to the size of the area of infarction.[4]

Thus a very useful diagnostic aid has been added to our armamentarium in the differential diagnosis of this important and extremely common clinical condition. It may well prove of paramount importance in instances where doubt exists as to diagnosis because of unusual circumstances such as lack of adequate history or important signs and laboratory findings. Particularly may this prove helpful where a dominant ECG pattern such as left bundle branch block obscures the changes of recent infarction.

Angina pectoris and the more prolonged myocardial ischæmia of coronary insufficiency (without infarction) do not result in rises of SGO-T activity.[12] Neither do pericarditis nor pulmonary infarction usually result in rises of SGO-T, but during the course of active rheumatic myocarditis about half the patients have some rise in SGO-T levels.[14]

The other clinical condition associated with marked increases in SGO-T activity is hepatitis, either infectious or toxic.[15] The extent of the rise is greater than in cardiac infarction and the increased activity is present for a longer period. Fortunately, there is little chance of confusing these two conditions clinically.

Finally, a word of caution is advisable. No laboratory procedure will ever supplant or supersede a careful history and clinical assessment of the patient. The procedure itself requires some care in setting up the equipment and standardizing the technique for each hospital laboratory, although a simplified method is described.[11] Also it must be borne in mind that transaminase is only one of several enzymes in tissue metabolism being studied at present and the last word has yet to be spoken on the subject.

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BODY POSITION AND THE MECHANICS OF BREATHING

New techniques have made it possible to measure the mechanical forces which are involved in breathing. There are two main factors, namely the elasticity of the lungs (or compliance) and the mechanical resistance of the lungs (or the resistance of the non-elastic tissues and the resistance to air flow through the tracheobronchial tree).

The lower the compliance the less easily distensible or "stiffer" are the lungs. The resistance of non-elastic tissues is due to friction which occurs during respiration in structures such as the thorax, diaphragm and abdominal contents. Airway resistance depends on the number, length and cross-sectional area of the tubes of the tracheo-bronchial tree. The higher the mechanical resistance the greater the effort required for respiration.

Compliance and mechanical resistance are calculated from measurements of intra-œsophageal pressures, air flow rates and volume changes made simultaneously and continuously throughout the respiratory cycle.

Attinger and his co-workers[1, 2] have used these methods to investigate the mechanics of breathing in different body positions (supine, sitting, prone, head down, and lateral). The subjects were divided into three groups, namely normal subjects, patients with chronic pulmonary emphysema and patients with a variety of cardiopulmonary diseases. In all subjects compliance or elasticity was highest and mechanical resistance lowest in the sitting position, as compared with the supine position. In patients with emphysema or other cardiopulmonary disease there was little difference between the supine and head down positions (elasticity was low and mechanical resistance high). The prone position showed results similar to the sitting position (compliance was high and mechanical resistance tended to be low). An increase in the respiratory rate made little difference to the mechanics of breathing in any of the positions studied in the normal subjects, but in the emphysema group in all positions there was a decrease in compliance. The cardiopulmonary disease group showed this decrease of compliance with rapid breathing, in the supine position only. In those patients with unilateral dysfunction, compliance was higher and mechanical resistance lower in the lateral position when the healthy lung was down, as compared with the diseased side down position. In one patient, with pleural effusion, removal of fluid resulted in an increase in elasticity and a decrease in mechanical resistance.

The changes in the mechanics of breathing when the supine position was adopted might be due to an increase in thoracic blood volume.

From these results it is apparent that breathing requires least effort in the sitting and prone positions. In the lateral position breathing should be easier if the healthy lung is in the down position. These changes are of little importance in normal subjects, but may cause striking effects when there is severe pulmonary insufficiency.

This research provides a physiological measurement for the dramatic improvement of dyspnœa in some patients when they adopt the sitting position, and it is apparent that patients with pulmonary insufficiency should be nursed in this position. The use of the prone position for thoracic surgery appears to be physiologically sound. On the other hand, the results suggest that the head down position will do little to improve ventilation in chronic pulmonary emphysema.

However, in certain patients the head down position may be advantageous. Cameron and his associates[3] have shown that in quadraplegics the vital capacity was best in the 20-degree head down position. In these patients all the inspiratory capacity was due to diaphragmatic movement; in the head down position the diaphragm was forced higher into the thoracic cavity by the weight of the abdominal viscera during expiration, and on inspiration the downward contraction of the diaphragm was greater.

These more complex investigations of basic pulmonary function are providing support and confirmation for many clinical observations. However, the reason for the difference in elasticity and mechanical resistance in different body positions is still largely a matter of conjecture.

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Medical News in brief

PALLIATION OF BREAST CANCER WITH PHOSPHORAMIDES

Bateman and Carlton of Washington, D.C., *(J.A.M.A.,* 162: 701, 1956) report studies on 122 cases of far advanced mammary cancer treated for from one to 24 months with one or both of two phosphoramides (N,N′,N″-triethylenethiophosphoramide and/or N-(3-oxapentamethylene)-N′,N″-diethylenephosphoramide). Of these, 117 patients had extensive primary or recurrent disease. Administration was by intravenous, intrapleural, intraperitoneal, intrapericardial, intratumour, intramuscular and oral routes. Wherever possible the phosphoramide was given into the tumour site. The intramuscular route was abandoned early in the series, and oral therapy was used only when it was impossible to give injections. For extensive disease, oral, intramuscular and sometimes intravenous administration proved inadequate. The total dose of triethylenethiosphoramide administered ranged from 15-1145 mg., and the duration of therapy from one to 103 weeks; the dose of oxapentamethylene ranged from 5-430 mg., and was given for from one to 37 weeks. Because of the hæmatological hazards of oxapentamethylene, most of the patients on this drug were subsequently given the other phosphoramide. Mostly, therapy was given at intervals of one to three weeks on outpatients.

Response to phosphoramides included healing of ulceration, regression of soft tissue masses, control of serous cavity effusions, recalcification of bone lesions and control of signs and symptoms of central nervous system metastases. It is concluded that the phosphoramides, particularly triethylenethiophosphoramide, are useful agents in prolonged palliation of advanced mammary carcinoma.

ACUTE GASTROINTESTINAL INFECTION IN INFANTS

Dr. Fortier and his colleagues from the Pædiatric Department of l'Hôpital de l'Enfant-Jésus, Quebec, *(Union méd., Canada,* 85: 1138, 1956) describe their studies in acute gastrointestinal infections of infancy. In 472 infants between the age of 15 days and 2½ years, they made a bacteriological study of the stools and of the nasopharyngeal secretions on the first day of hospitalization. Seventy-four of the children were suffering from acute diarrhœa on admission, whereas another 108 developed an acute diarrhœa while in hospital. The control group without digestive disturbances numbered 290. In the stools they found that the commonest pathogen was *Proteus vulgaris* with, in order, *Aerobacter aerogenes,* pneumococcus, *E. Coli* and staphylococcus as other residents of the bowel. On 40 occasions staphylococci were found in both nasopharynx and intestine; on 17 occasions pneumococci were found at both sites. Other children harboured staphylococci or pneumococci in the nasopharynx without corresponding intestinal infection. The role of all these organisms in the etiology of acute diarrhœa in infancy is of course still undetermined.

The authors indicate their satisfaction with dietetic treatment of the acute diarrhœas starting in the acute stage with Arobon (a carob flour preparation) and going on to Eledon (powdered buttermilk) and Pelargon (powdered acidified whole milk). Many of the children involved in the study were put on this type of diet, which appeared to give good results regardless of the causative microorganism in the intestine.

MENTALLY DEFECTIVE BABIES

A plea was recently made in this *Journal* for the nursing and management of mentally defective babies by their own mothers, rather than in an institution. It is interesting to note that the same view is put forward in a recent article by Smith in the *South African Medical Journal* (30: 881, 1956). Smith discusses two cases of mental deficiency in which the pædiatrician or family doctor advised the parents to have the baby certified, and the parents followed the advice; both parties no doubt honestly believed this to be the best course and the best management in the light of modern medical practice. Smith, however, concludes that the mother is nearly always the best nurse for such a child and the best place is at home. He points up the grave responsibility of the family doctor in these cases by saying, "Whether the parents will reject or accept their child emotionally, will depend largely on the mental set induced in them by suggestions emanating from the family doctor or pædiatrician. In most cases, suitable guidance should go a long way towards helping the parents to view their child's disability objectively, to accept it as it is, and to build up a healthy, positive attitude to it."

AGE, SEX AND SERUM LIPIDS

Adlersberg and his colleagues from New York *(J.A.M.A.,* 162: 619, 1956) have studied the serum cholesterol and phospholipid values in the serum of 1,200 specimens obtained from healthy males and females between the ages of two and 77 years. Persons involved were a healthy group of industrial workers and their dependents in the low-middle income group. The main point emerging from the results is that whereas in the 28-32 age group the average serum cholesterol value was much higher in men than in women, the difference was reversed over the age of 50. Both cholesterol and phospholipid values in males remained constant up to age 19, increased from 20 to 33 and then remained constant to age 60, whereas in women the values remained constant to age 32 and then increased sharply to age 58. It is suggested that the increase in values in males between 20 and 33 plays a part in producing the higher incidence of coronary artery disease in younger males, and that the increasing incidence of the disease in older females after the menopause is related to the analogous changes occurring in women and starting 13 years later and lasting 12 years longer than in men.

(Continued on advertising page 50)

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REVIEW ARTICLE

A REVIEW OF ABNORMAL CALCIUM AND PHOSPHORUS METABOLISM

PART I. HYPERCALCÆMIA

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THE NORMAL DISTRIBUTION, metabolism and physiological effects of calcium and phosphorus have been reviewed by the authors in a previous paper.[29] We shall now deal with those important abnormal states characterized by *hypercalcæmia*. The following outline may serve as a guide:

ETIOLOGY OF HYPERCALCÆMIA

1. Excessive Intake—oral or parenteral.
2. Hypervitaminosis D.
3. Administration of Dihydrotachysterol (AT-10).
4. Parathyroid Poisoning.
5. Milk-Alkali Syndrome.
6. Primary and Secondary Skeletal Neoplasms (excluding multiple myeloma and Paget's disease).
7. Immobilization.
8. Multiple Myeloma.
9. Paget's Disease.
10. Boeck's Sarcoidosis.
11. Administration of Anterior Pituitary Extracts.
12. Administration of Gonadotrophic Hormones and Œstrogens.
13. Occasionally in Advanced Nephritis with Uræmia.
14. Leukæmia and Polycythæmia.
15. Primary Hyperparathyroidism.
    A. Pathogenesis.
    B. Signs and Symptoms.
    C. Tests.
    D. Differential Diagnosis.
    E. Treatment.

An *elevated* plasma calcium may be found in a variety of abnormal conditions. It may be due to an excessive intake or to factors which increase the absorption, to endocrine or metabolic upsets, or to bone diseases. The essential signs and symptoms of a hypercalcæmia will be subsequently considered.

1. An *excessive dietary intake* of calcium and phosphorus will lead to a raised serum calcium level which reaches a maximum in 2-3 hours and returns to a preabsorptive level within 4 hours. After an intravenous injection the maximal level is reached in 2-3 minutes and returns to normal levels in 2-3 hours. With the use of calcium gluconate for example, intramuscularly, a maximum rise is obtained in 1 hour, falling to normal levels in 3-4 hours.

2. The excessive administration of vitamin D—over 30,000 international units per day in infants, over 50,000 international units per day in children, and about 150,000 international units per day in adults—can produce nephrolithiasis or nephrocalcinosis and/or metastatic calcification. It goes without saying that *hypervitaminosis D* is made much worse if the calcium and phosphorus intake has also been excessive. In the presence of hypercalcæmia the following symptoms may be present: (1) weakness, (2) anorexia, (3) loss of weight, (4) headache, (5) nausea, (6) vomiting, (7) dryness in nose and throat, (8) difficulty in focusing the eyes, (9) difficulty in swallowing, (10) polyuria, (11) urinary frequency, (12) hyposthenuria, (13) polydipsia, (14) hypotonia, (15) hypercalcinuria and hyperphosphaturia, (16) band-keratitis, and (17) a shortened Q-T interval in the electrocardiogram.

3. The *administration of dihydrotachysterol* (AT-10) will also cause a rise in the plasma calcium. Its action resembles that of the parathyroid hormone more than that of vitamin D.[29]

4. A similar picture results when *parathyroid poisoning* occurs. The latter refers to the marked toxic effects of hyperparathyroidism, which occurs when the serum calcium level rises above 17 mg. %. If bone disease is very advanced in this condition, one may be tempted to prescribe a high calcium diet. This may push the calcium level above the critical level of 17 mg. %. The high plasma calcium results in inspissation of the blood, acute renal filtration failure, a rapidly rising serum phosphorus and non-protein nitrogen (NPN); the combination causes the precipitation of calcium phosphate in the tissues, especially in the lungs, stomach, and kidneys, with necrosis of the calcified areas and chemical death.

5. The *milk-alkali syndrome*[1] has been described, from the prolonged and excessive intake of milk and alkali. This may be seen in the treatment of peptic ulcer with milk and absorbable alkalis such as Sippy powders (calcium carbonate and magnesium oxide). In 1936, Cope[2B] reported four cases of alkalosis with a hypercalcæmia complicating the treatment of gastric ulcer with alkaline powders. A reversion to normal blood levels occurred 10 days after cessation of therapy. Burnett *et al.*[2A] reported, in 1949, six cases presenting with hypercalcæmia without hypercalcinuria, a normal or high serum phosphorus, "but not depressed", impaired renal function with retention of NPN, decreased excretion of phenolsulphonphthalein, and a fixed specific gravity of the urine, calcium deposits in the conjunctivæ, and band-keratitis at the periphery of the cornea. When these patients were placed on a low calcium diet, they showed marked improvement with a lowering of the serum calcium. Their cases did not show a marked alkalosis.

6. In *primary and secondary skeletal neoplasms*, the serum calcium may be elevated but it is often normal. Values up to 24 mg. % and more have been observed if the sarcoma or the

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metastases are widespread. The plasma phosphorus and alkaline phosphatase are normal unless increased osteoblastic activity is present, as in osteogenic sarcoma—in which case the alkaline phosphatase activity is raised. It should be remembered that in mammary carcinoma with bone metastases, fatal hypercalcæmia has been reported when large doses of œstrogens and androgens were given.

7. In *immobilization* as in paraplegia or in fractures, one occasionally detects an elevated plasma calcium, especially in the first 3-4 weeks when bone reabsorption is at a height and osteoporosis is developing. This is especially true in the osteoporosis which rapidly develops in children who are immobilized. The phosphorus levels in these patients may be normal or raised. Later on, when appropriate therapy has been instituted, and when healing and mobilization have taken place, levels may be considerably lower because of the increased utilization of calcium and phosphorus (hungry bones).

8. In *multiple myeloma,* over 50% of patients have an elevated plasma calcium, and values approaching 20 mg. % have been reported. This is probably due to bone resorption although the cause is not clear. Since the parathyroids are frequently enlarged in multiple myeloma, these glands have been incriminated. But since there is no generalized bone destruction and the plasma phosphorus and phosphatase activities are normal, this is not likely. The rise is not due to hyperproteinæmia, for the globulins and not the albumins are elevated. It is the albumins which are associated with the non-diffusible calcium fraction and which are in fact often lowered in multiple myeloma.

9. In *Paget's disease,* if an involved bone is immobilized the stimulus to bone formation ceases and destruction continues. As the kidneys are unable to handle all the calcium presented to them in a given time, hypercalcæmia and hypercalcinuria will be present.

10. A hypercalcæmia, high serum phosphatase levels, hypercalcinuria and kidney stones occur in a small proportion of patients with *Boeck's sarcoidosis,* and occasionally this syndrome is confused with hyperparathyroidism.

Dent, Flynn and Nabarro[3] described the dramatic effect of cortisone on the plasma calcium levels, on the hypercalcæmic symptoms and on renal function in patients with Boeck's sarcoid. Anderson *et al.*[4] have confirmed the cortisone effect in their metabolic studies on three patients.

Patients with Boeck's sarcoid who had a hypercalcæmia showed the clinical manifestations of a raised plasma calcium—fatigue, weakness, anorexia, nausea, vomiting, weight loss, polyuria and polydipsia, proteinuria, renal failure and band-keratitis of the cornea.

The hypercalcæmia was supposedly associated with a hyperproteinæmia, but the rise in plasma calcium was shown to be greater than could be accounted for by the increase in protein, which in any case was not albumin. Others suggested an associated hyperparathyroid activity, or from active destruction of bone sarcoid deposits, or that less endogenous calcium was excreted into the fæces. Parathyroid hyperplasia was reported in some but not in all cases of sarcoidosis with a hypercalcæmia.[5, 6] In the three cases reported and studied by Anderson *et al.,* operative explorations were carried out but no parathyroid enlargements were found. No cases of sarcoid were reported with a low plasma phosphorus, which is strong evidence against parathyroid over-activity.

Because of the rapid response of such cases to cortisone, Dent *et al.* in 1953 felt that the hypercalcæmia was due to bone destruction. In advanced renal failure, a decreased ability to excrete calcium as fast as it is presented may be another factor.

It seems that in Anderson's three cases there was a greatly increased absorption of calcium from the gastrointestinal tract, and a given dose of calciferol resulted in a much greater absorption of calcium than in normals. The increased absorption might be due to an increased intake of vitamin D or to an increased sensitivity to a normal intake of vitamin D. In the three cases studied, a close resemblance to a vitamin D action was also seen from the abnormally large urinary excretions, suggesting that reabsorption by the renal tubules was decreased. There is much evidence which suggests that vitamin D does decrease tubular reabsorption.[7] This was discussed in our previous paper.[29]

Anderson found that a diminished intake resulted in a decreased absorption and a decreased plasma calcium level. When cortisone was administered, the fæcal calcium content increased, the plasma calcium fell and the urinary calcium diminished more slowly. Hence it appeared as though cortisone reversed the metabolic defect and acted antagonistically to vitamin D, to which these patients seemed to be abnormally sensitive. If this antagonistic action occurs as a more general phenomenon, patients with Cushing's disease or syndrome should absorb very little calcium from the gastrointestinal tract. This appears to be so, according to the metabolic data of Freyberg and Grant[8] in 1936, and of Soffer, Gabrilove and Jailer[9] in 1950. Calcium absorption from the bowel was indeed very low, and when Freyberg's cases received large doses of vitamin D, no increased calcium absorption was detected. Absorption of calcium was also poor when high calcium diets were given.

Cortisone increases the requirements of vitamin D. Moehlig and Steinbach[10] reported that hypoparathyroid patients, already well controlled on tachysterol, when treated with cortisone for multiple osteoarthritis, developed tetany in spite of a large intake of calcium and vitamin D. They also reported on a patient with

sprue who when given cortisone developed tetany not completely relieved by oral or intravenous calcium. Colcher, Drachman and Adlersberg[11] reported overt tetany in 3 cases treated with cortisone and ACTH for intractable sprue.

It is suggested that cortisone and vitamin D act antagonistically by virtue of a mechanism of competitive inhibition. The general resemblance between their molecular structures may account for this action. If this is so, many clinical possibilities become evident.

Cortisone may be worth a trial in cases of vitamin D poisoning and in other cases of overabsorption and in idiopathic hypercalcinuria of infancy. Albright and his group reported at the New York Academy of Science meetings held in January 1956 in New York the successful use of phytic acid administered orally to one case of idiopathic hypercalcinuria.

Cortisone may also be of value in the differential diagnosis of hypercalcæmia due to hyperparathyroidism and to sarcoidosis. In hyperparathyroidism, 150 mg. of cortisone per day does not alter the plasma calcium, but in sarcoidosis it does cause a fall, with resultant improvement in renal function and a decline in the nonprotein nitrogen (NPN). In any case, patients with sarcoidosis are differentiated by the frequent absence of a hypophosphatæmia, by the presence of a hyperproteinæmia, by the absence of generalized decalcified bone lesions, and if present, by bone lesions usually confined to the hands and feet.

11. Cantarow[12] has reported that the administration of *anterior pituitary extracts* to animals has resulted in a hypercalcæmia. This has been said to be due to a "parathyrotropic factor". However, except for this possibility a hypercalcæmia has not been observed in uncomplicated cases of pituitary disorders. Borderline high values have occasionally occurred in pituitary basophilism. Reference will again be made to this in the discussion on primary hyperparathyroidism.

12. After administration of *gonadotrophic hormone* and certain œstrogens such as œstrone, alpha-œstradiol benzoate, and œstriol to experimental animals, raised calcium levels have developed. These effects are probably exerted directly on bone matrix metabolism rather than on the parathyroid gland *per se*.[29]

13. In rare cases of advanced *nephritis* with uræmia, a hypercalcæmia may develop. This has been said to be due to a secondary hyperparathyroidism. It is however more common to observe a lowered plasma calcium level, as renal acidosis causes an increased calcium excretion, and because calcium tends to be precipitated due to the retention of acid radicals in the blood when glomerular disease is present along with tubular malfunction.

14. Still obscure is the hypercalcæmia which can be present *per se* in cases of *leukæmia* and *polycythæmia*.

15. PRIMARY HYPERPARATHYROIDISM

A. *Pathogenesis*

Five to 10 per cent of all kidney stones may be associated with parathyroid hyperfunction. It most frequently occurs in middle life, and about 70% of the reported cases are in females. It can occur without evidence of bone disease, it is relatively common if searched for, and involvement of the urinary tract is described more often than bone involvement.

In 88% of the cases the lesions are adenomata, involving a part or the whole of one of the two to ten glands normally present, and occasionally they may be malignant. The cause of the adenomata is unknown; a long history of poor calcium intake ultimately leading to the stimulation of all parathyroid tissue may be a factor. Erdheim[13] in 1907 described germinative centres in hyperplastic parathyroid glands, and the question arises and remains unanswered: does hyperplasia exist before adenomata develop and is there a sudden release of one or more of the germinative centres from control to form adenomas or carcinomas?

Hypertrophy and hyperplasia, a much rarer cause, are secondary to disease of other organs such as the kidneys. This may be seen in rickets in children or in osteomalacia in adults, in pregnancy, in renal insufficiency with phosphate retention, and in cases of inadequate calcium intake. While hyperplasia may be present, there may be no hyperparathyroidism. Houssay[14] in 1936 showed that dogs with pituitary insufficiency or with pancreatic deficiency had atrophic parathyroids. The serum calcium was low and the phosphorus was elevated when the pancreas was hypofunctioning. Insulin prevented a fall in the serum calcium in these cases. In patients with pituitary insufficiency, it was shown that the serum calcium remained unchanged and that the administration of anterior pituitary extract increased the size of the parathyroid glands. Hertz and Kranes[15] confirmed the effect of anterior pituitary extract upon the parathyroids. Cushing and Davidoff,[16] Claude and Baudouin[17] and Erdheim[18] reported parathyroid enlargement in acromegalics and in cases of pituitary eosinophilic tumour. Schmorl[19] and Molineus[20] reported on a case of hyperparathyroidism with osteitis fibrosa generalisata and a large basophil tumour. Shelburne and McLaughlin[21] and Lloyd[22] reported cases of pituitary tumours associated with islet cell enlargement of the pancreas (with or without hyperinsulinism) and hyperparathyroidism. In 1947 Kepler, Rynearson, Sprague and Keating reported two cases of hyperparathyroidism associated with pituitary and pancreatic islet cell tumours.

In acromegalics the plasma phosphorus is elevated but the serum calcium is not and the phosphatase activity is normal. Hence it may

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be assumed that the osteoporotic bone lesions probably are not due to hyperparathyroidism. Of course with acromegaly, all tissues are enlarged and there is no reason why the parathyroids should not be as well. The demineralization of bone might be better explained as follows: eosinophilic tumours cause adrenal hypertrophy with an increased production of glucocorticoids. The latter steroids by virtue of their anti-anabolic and/or catabolic effect on protein cause, amongst other things, osteoporosis. If calcium absorption from the gut is also decreased[23, 29] the bone lesions become more severe. These tumours also cause thyroid hypertrophy and ultimately a relative protein deficiency to a greater or lesser extent. The fact that acromegalics use much protein for growth means that there is less available for bone matrix formation, and so the tendency towards osteoporosis is increased.

Whether the parathyroid secretes one, two or three hormones remains undecided. It is suggested by some that one hormone may act on the kidney, one on the bones and a third on skin directly. The skin effects become manifest when the hormone is deficient, as in spontaneous hypoparathyroidism in children.

B. *The signs and symptoms*

The signs and symptoms of hyperparathyroidism may be divided into those due to (a) hypercalcæmia *per se,* (b) bone disease, (c) urinary tract complications, and (d) decreased hæmatopoietic function. Calcium levels up to 12 mg. % may be seen and the inorganic phosphorus level tends to stay below 3 mg. % unless renal damage prevents this drop. If bone damage is extensive, the increased stresses and strains placed upon the skeletal system in mobilization will raise the alkaline phosphatase to the order of 30 Bodansky units. Calcium may be deposited not only in the kidneys, but also in the lungs and gastric mucosa (where acid is lost), in the soft tissues about joints, and in the media of arteries (Mönckeberg's medial sclerosis).

(a) Hypercalcæmia decreases intestinal motility and may result in anorexia, nausea and vomiting, loss of appetite with subsequent headache, and loss of weight. Such patients will also have dryness of the nose and throat, difficulty in swallowing, muscle weakness, hypotonia, decreased auditory acuity, difficulty in focusing the eyes, band-keratitis of the cornea and a shortened Q-T interval in the electrocardiogram.

(b) Bone disorders are by no means an essential feature even in severe hyperparathyroidism. They vary from a generalized decalcification to superimposed cysts and tumours. This condition has been called "osteitis fibrosa generalisata of von Recklinghausen" or "osteitis fibrosa cystica". Hence, there may be no bone lesion or there may be almost complete decalcification and death due to paralysis of the respiratory muscles. When there is severe decalcification, the bones may be cut with a knife.

In some cases of hyperparathyroidism instead of the above bone lesions an osteoporotic form occurs, difficult to differentiate from the bone lesions observed in senile osteoporosis, osteomalacia or hyperthyroidism.[30]

The pain, which is a frequent and prominent feature with such bone disease, quickly disappears after the removal of the parathyroid adenoma—even before there is x-ray evidence of recalcification. Deformities include long bone bending, kyphosis, pigeon-breast deformity of the chest with crushed codfish-type vertebræ, the disappearance of the neck into the thorax and pelvic distortion as in osteomalacia, which results in a limp and waddling gait. Schmorl's nodes are seen in the x-ray and are due to the herniation of the nuclei pulposi through the endplates of the vertebræ. Since the main defect is one of thinned bone, spontaneous fractures are common, whereas in osteomalacia where calcium is deficient bending occurs.

The bone cysts that may appear are areas of soft tissues, perhaps of bone tumour tissue which has degenerated, producing a liquid-filled centre and surrounded by a fibrous tissue capsule. The bone tumours are composed of supporting bone marrow cells plus osteoblasts and osteoclasts. These tumours, frequently confused with malignancies, produce symptoms including pain because of their expansion or because they help to weaken the bones, thus aiding in the production of spontaneous fractures. The sites of predilection of these tumours are the jaws (producing a giant cell tumour—epulis), the ends of long bones, the metacarpals and the metatarsals. On x-ray a generalized decalcification is seen, the lamina dura of the teeth is often absent, the skull appears ground-glass-like because it is thin and porotic, producing a finely mottled appearance, and cysts and tumours may be found if sought for. Pseudocysts are areas of thin trabeculæ plus fibrous tissue which give a cystic appearance and disappear radiologically with the bone tumours, when the disease is cured.

(c) These patients, because of the hypercalcæmia, develop a hypercalcinuria and a hyperphosphaturia. This results in the withdrawal of much salt and water; therefore polyuria, increased frequency and, later on, a polydipsia develop. Because much water is withdrawn, the urine tends to become hyposthenuric. Of course polyuria may occur solely on the basis of renal tubular damage as in nephrocalcinosis, which may be present and yet not seen in x-ray. The diagnosis of diabetes insipidus might be made in error.

The urinary tract complications may be due to nephrolithiasis with perhaps partial or complete obstruction and an ascending type of pyelonephritis. Albumin, casts, blood and crystals may be found in the urine. One of the first symptoms to appear in hyperparathyroidism may be renal colic even before the bone lesions become manifest. Because of the increased urinary excretion of calcium and phosphorus, the stones are predominantly composed of calcium phosphate and to a lesser extent calcium oxalate. With a superimposed infection and an alkaline urine, the stone becomes coated with a mixture of magnesium ammonium phosphate and calcium phosphate.

Radiographs of these stones may reveal their structural pattern and identification. This knowledge may be useful when therapy is instituted. Calcium oxalate stones have a crystalline structure with radiations from a central point, whereas phosphate stones with or without magnesium grow by concentric layers. Cystine stones are homogeneous and grow by the fusing of smaller components. Uric acid stones cannot be picked up by radiographs. While patients may pass calcium phosphate "sand", it is interesting that only phosphate and cystine stones become staghorn in structure.

A more serious development of hypercalcæmia is nephrocalcinosis, in which deposits of calcium are found in the renal parenchyma, in and about the collecting tubules. Albright and Reifenstein feel that if nephrocalcinosis is present, nephrolithiasis is infrequent in the same patient and vice versa. The tubules get plugged with calcium phosphate and other mineral containing casts and some of these appear in the urine. If the urine be alkaline, such casts can be found in any case of hypercalcinuria and will probably disappear with acidification.

Already mentioned are the occasional rare cases of acute hyperparathyroidism in which poisoning occurs. Death in such cases is due not only to inspissation of calcium in kidneys with renal failure and to hypercalcæmia *per se*, but also to circulatory collapse. The marked depletion of plasma sodium and chloride because of the polyuria contributes to the renal and circulatory failure.

(d) When bone disease is present, there is often a marked fibrosis of the marrow, frequently causing a leukopenia with or without an anæmia. On the other hand, a hypoplastic anæmia may develop due to renal impairment.

To reëmphasize, if the calcium intake is adequate, bone disease need never appear.

If a patient has urinary calculi, bone disease, or symptoms which may fit in with hypercalcæmia, hyperparathyroidism must be considered as a possible cause. The plasma calcium is elevated and the phosphorus is lowered, and perhaps only in multiple myeloma and secondary carcinoma of the bones are such electrolyte levels seen. The alkaline phosphate levels may be normal or elevated. A rise indicates the amount of bone disease—for the more the destruction, the more will be the stresses placed on the bones, resulting in an increased osteoblastic activity. If on the other hand the x-rays reveal much bone destruction and the alkaline phosphatase is normal, hyperparathyroidism is unlikely. The diagnosis of primary hyperparathyroidism is made more difficult if secondary renal functional impairment develops; for in such a case the plasma phosphorus will rise and the calcium fall. It then becomes important to have a history which reveals bone disease before the development of renal impairment.

C. *Tests*

(a) The Sulkowitch test for urinary calcium is a useful diagnostic aid, for it may be positive even though the blood levels of calcium and phosphorus be normal. Many patients may have a normal or near normal calcium plasma level despite repeated analyses and some of these cases may be due to a hypoproteinæmia. When this happens, it is important to check the serum protein level and make the appropriate allowance, for an increased ionized calcium concentration may be marked. Ionized calcium concentration can be determined from the monograms of McLean and Hastings.[24]

(b) Another test which may prove useful is the one used by Albright and Reifenstein. Patients are put on 125 mg. of calcium per day for seven days. An excretion of 150 mg. calcium for a 24-hour period is high and a figure of 200 mg. for 24 hours is very high, and hyperparathyroidism is a likely diagnosis. Of course urinary excretion may be persistently high if the patient is immobilized or has endocrine disease such as Cushing's syndrome or thyrotoxicosis.

(c) Howard, Hopkins and Connor[25A,25B] used intravenous calcium as a measure of the activity of the parathyroid glands. They gave 8-30 mg. (average 15 mg.) of calcium gluconate per kilogram of body weight intravenously over a 4-hour period to a group of normal persons, to patients with hyperparathyroidism due to parathyroid adenomata, and to patients developing hypoparathyroidism subsequent to thyroidectomy. The serum and urinary calcium and inorganic phosphorus levels were checked prior to the test as a control and during the test periods. Normal subjects responded by a rise in serum phosphorus and a decline in urine concentration. In the hyperparathyroid group the serum phosphorus was unchanged and there was either no change or a slight rise in the urinary excretion of phosphorus. In the hypoparathyroid group the serum phosphorus was little altered but there was a marked rise in the urinary excretion of this electrolyte. The authors postulated that the results obtained in normals were due to the hypercalcæmia, which depressed normal para-

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thyroids but did not affect overactive relatively autonomous parathyroid adenomata. Obviously, in the hypoparathyroid patients, since there is little functioning tissue, one would not expect calcium to exert much action. However, it is interesting to note that the urinary phosphorus rose to higher levels in the hypoparathyroid state than in the adenomatous condition. This would suggest a possible direct action of calcium on the kidney tending to increase phosphorus excretion. In conclusion, one might postulate that a rising serum calcium could affect the excretion of phosphorus in two directions. The rising serum calcium exerts an inhibiting effect on the parathyroids and so tends to diminish the urinary phosphorus excretion; whereas a direct renal effect tends to increase the urinary phosphorus excretion either by decreasing the tubular reabsorption of phosphorus or the increased urinary calcium excretion drags more phosphorus with it.

Kyle, Erdman and Schaaf[26] placed patients on a constant intake of calcium and phosphorus. Serum and urine were collected before and after the intravenous infusion of calcium gluconate. In patients without bone disease the serum calcium level rose sharply during the infusion and about 60% of the infused calcium was retained. The urinary phosphorus excretion decreased during the infusion and in most cases the decreased excretion was reflected in a 24-hour collection period. The serum phosphorus level rose about 40% and remained elevated for several hours.

In two patients with hypoparathyroidism a marked rise in the phosphorus excretion accompanied the infusion of calcium. In one instance of functioning parathyroid tumour, there was a minimal rise in the serum phosphorus level and no diminution in phosphorus excretion. Although very large amounts of infused calcium were retained in osteomalacia, patients with osteoporosis demonstrated a degree of calcium excretion comparable with that which occurs in normal persons.

(d) Schilling and Laszlo[27] measured the rates of urinary calcium excretion following its intravenous administration as an indicator of bone metabolism. The procedure, which is unwieldy, requires many catheter as well as voided urine samples, plus 12 blood samples of which six are obtained by an indwelling Cournand needle in the femoral artery. They found that the rate of excretion of calcium was subnormal in patients with an increased tendency to bone deposition. Increased rates were found in patients with osteolytic activity. They stated that the good correlation between these data and metabolic balance studies suggests the usefulness of this test in defining the state of skeletal activity and the effects of therapy thereon.

D. *The differential diagnosis of primary hyperparathyroidism*

1. *Osteoporosis* is basically too little bone formation, due to a deficiency of bone matrix formation. Meanwhile bone resorption continues. The process is usually slow but progressive and while a hypercalcinuria can be detected from time to time, ordinarily the plasma levels of calcium and phosphorus are normal. If the process be acute as in immobilized children, or in patients suffering from rheumatoid arthritis on cortisone or ACTH therapy, a marked rise in the plasma calcium and phosphorus levels may occur, with an increased urinary excretion. The alkaline phosphatase level is low or normal. Osteoporosis is the only metabolic disorder with a markedly diminished bone density and a normal alkaline phosphatase activity. Osteoblastic activity is at a minimum. In this condition parts of the vertebræ and pelvis may be destroyed. The skull and the lamina dura are rarely affected and no bone cysts or tumours are found.

2. *Osteomalacia* is that form of too little bone formation due to a deficiency of calcium, either because of a vitamin D deficiency, inadequate calcium intake or poor absorption as in steatorrhœa. Renal tubular functional impairment without glomerular disease may also be a cause. Generalized decalcification showing as increased transparency of bone is seen in x-ray. Tumours and cysts are rare findings in such bones, and bending rather than fracture deformities are described. Milkman's pseudofractures may be seen radiologically. The plasma and urine calcium and phosphorus are low but the alkaline phosphatase activity is increased because of the increased stresses and strains put on the thinned bones. Actually in the early phases of osteomalacia where parathyroid compensation is nil, the plasma calcium is low and the phosphorus normal. When there is partial compensation both elements are low, and when parathyroid compensation is complete the plasma calcium is normal and the phosphorus is low. Juvenile rickets is the same as adult osteomalacia. Renal rickets however is a misnomer, for it is not rickets but an "osteitis fibrosa generalisata" which develops when both glomerular and tubular renal functional impairment are present.

3. *Osteogenesis imperfecta* is a dominant hereditary disease which seems to involve mesenchymal tissue and in which an inborn error in the metabolism of copper seems to be involved. These tissues do not develop fully, and despite osteoblastic activity an adequate bone matrix is not laid down. Whatever bone is formed is found to be brittle, and often the thickest parts fracture, whereas in hyperparathyroidism the thinnest portions are likely to break.

The subcutaneous tissues of such patients are thin. This accounts for the blue scleræ in that the choroid shows through.

The bone lesions are similar to those of osteoporosis, the skull is thin but not decalcified, and the lamina dura is intact. The plasma calcium and phosphorus are normal but the alkaline phosphatase is raised. Fractures are frequent and otosclerosis may be present. Death is the rule when the condition is severe. If the patient lives until adolescence, osteosclerosis develops and the prognosis is better.

4. *Polyostotic fibrous dysplasia* (Albright's syndrome) is a localized non-metabolic and non-hormonal type of bone disease, and may be confused with hyperparathyroidism.

The lesions are hyperostotic and hypoostotic in a segmental distribution with brown cutaneous pigmentation. In females, sexual and somatic precocity is observed. However, precocity and brown pigmentation are not necessarily a constant finding in this sex. The skull, metatarsals, metacarpals, phalanges and upper ends of the tibiæ and femora are sites of predilection. The disease can affect one limb or a part of the limb and not another. The upper end of the femur if affected bows outwards, producing a "shepherd's crook" deformity.

The serum calcium and phosphorus levels are normal, and the alkaline phosphatase may be elevated.

5. *Paget's disease* presents in the radiograph with sharply demarcated lesions with coarse trabeculæ, and with bony expansions and overgrowths. It is a "localized" form of bone disease and the calcium and phosphorus levels are normal. The alkaline phosphatase is elevated. Here, it seems that the initial lesion is bone destruction with attempts at repair. This process of destruction and repair can recur many times, producing a bizarre and architecturally poor structure susceptible to fracture. The osteoid seams are wide and irregular, and overgrowth of bone with thickened cortices is frequently seen.

6. *Solitary bone cysts, i.e. osteitis fibrosa localisata*, need never be confused with hyperparathyroidism. It is often diagnosed radiologically as a cyst. Its usual site of predilection is at the end of long bones (at the upper end of the femur), and this may lead to pathological fractures.

7. *Multiple myeloma* in radiographs may look like osteitis fibrosa generalisata, but in multiple myeloma the lesions show sharply punched out areas, and in 50% of cases the plasma calcium level is elevated, as is the urinary calcium excretion. The phosphorus and alkaline phosphatase are usually normal, although occasionally low phosphorus values have been obtained. The alkaline phosphatase is rarely if ever elevated. The diagnosis is aided by the finding of Bence-Jones proteinuria and/or a hyperglobulinæmia. Plasma cells may be detected in the peripheral blood or by a sternal marrow puncture.

8. *Metastatic lesions* have already been discussed in reference to producing an elevated plasma and urine calcium. The bone lesions are variable, and osteoporotic as well as osteosclerotic lesions are seen.

9. *Hypervitaminosis D and hypercalcæmia* with the excessive intake of milk and alkalis have already been discussed. The hypercalcæmia may erroneously suggest the diagnosis of hyperparathyroidism.

10. *Generalized skeletal xanthomatoses.* The Hand-Schüller-Christian syndrome, and Gaucher and Niemann-Pick disease can cause bone lesions due to eosinophilic granulomatous infiltrations. The calcium and phosphorus levels are usually normal. In Gaucher and Niemann-Pick disease there is involvement of lymph nodes, pigmentation, hepatitis, splenomegaly and pulmonary lesions. Lipid containing cells are obtained on marrow or splenic puncture.

E. *The treatment*

The treatment of primary hyperparathyroidism consists of forcing fluids, decreasing the milk intake, and the surgical exploration of the parathyroid glands for adenomata or hyperplasias. Preoperatively and postoperatively calcium should be given to prevent tetany, which might develop when a part or all of the parathyroids are removed. It is wise not to remove all the parathyroid glands when permanent renal damage is present, because with phosphate retention, tetanic levels of calcium may persist permanently.

Postoperatively 1-1.5 g. of calcium should be given per day and 0.75-1 g. of phosphorus. The calcium may be given in the form of 10-25 g. of calcium gluconate, 10-15 g. of calcium lactate, or an equivalent amount of calcium acid phosphate. If tetany is likely to develop, one should administer phosphorus cautiously. No magnesium should ever be given, for it will tend to lower the plasma calcium level even more.

In cases of idiopathic hypercalcinuria of infancy, and in hypervitaminosis D as well as in the other hypercalcæmic states, cortisone and sodium phytate may be worth a trial. In one case of idiopathic hypercalcinuria of infancy on a low calcium intake, Albright used a 15% solution of sodium phytate orally in divided doses. The urine calcium dropped from 150 to 60 mg. per 24 hours. The suggested dose is 9-18 g. per day given in divided doses after meals. A dose lower than 5 g. per day exerted no physiological effect. All patients on sodium phytate developed an initial temporary diarrhœa. When 18-25 or more grams of this salt are given, anorexia, nausea, vomiting and an intense diarrhœa develop. It is believed that the mechanism of action is due to the displacement of sodium by calcium ions. The net result is a binding of calcium ions in an insoluble unabsorbable form, with a consequent rise in the stool calcium.

There is no place in the routine treatment of hypercalcæmia in primary hyperparathyroidism, or indeed in any case of severe hypercalcæmia, for use of chelating agents such as sodium ethylene diamine tetraacetate (sodium EDTA), until its toxic effects have been fully investigated. Dudley *et al.*[28] reported on the autopsy findings of two cases of hypercalcæmia given sodium EDTA intravenously. In one case the hypercalcæmia was due to malignant bone metastases and the other case was of a child with acute hypercalcæmia after vitamin D therapy. Severe renal tubular damage, especially to the proximal convoluted tubules, engorgement of the reticuloendothelial cells with coarse eosinophilic granules, and hæmorrhagic manifestations were seen. These findings have never been previously reported as purely due to hypercalcæmia.

Sodium EDTA does not seem to hold calcium avidly and when it is administered the urine must be kept alkaline. In any case the agent does not seem to increase significantly the urinary calcium excretion. Even so, in the renal passage of this drug an increased acidity is produced and much calcium is released into the tubules. This may explain the observed necrotizing effect.

On the other hand, when sodium or calcium EDTA is used for lead and other heavy metal poisoning, the toxic metals are strongly bound and their urinary excretion does markedly rise, with a resultant decrease in toxicity to the patient.

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PUBLIC RELATIONS FORUM

Conducted by L. W. HOLMES,
Assistant Secretary, C.M.A.

PUBLIC ATTITUDES TOWARDS DOCTORS. III.

THIS IS THE THIRD in a series of articles reviewing the results of a public opinion survey conducted for the American Medical Association. Public and professional views on medical economics are discussed in this article.

VIEWS ABOUT MEDICAL ECONOMICS

Is the public as critical of the economic side of medicine as some people think? To gauge opinion on medical costs the survey included a number of economic questions which revealed:

Individual doctors' charges receive only moderate criticism by the public.

Questions phrased about "my doctor" and "most doctors" (reported on earlier) brought out the fact that only 16% of the public believe their own doctors charge too much while 43% say most doctors' fees are too high. It was also shown that only 13% think their own doctor's charges have gone up faster than other living costs while 35% say this is true of most doctors' fees. Ninety per cent deny their own doctors plan to get rich quick and 70% deny most doctors do. Doctors themselves express the opinion that their charges are that aspect of medicine of which the public is most critical.

People think their own doctors do not make too much money and only about one-third of the public think most doctors do.

Two-thirds of the public deny that "compared with his patients" their own doctors make too much money. When asked, "What about him gives you the idea that he makes too much money?", only 13% mention any reasons. Four per cent say, "because he lives well, has luxuries"; another 4% mention "his charges";

2% say they draw this conclusion because of the number of patients he has, and 1% say "because he has money". About one-third of the public (38%) say they think that "most doctors" make too much money, but 44% deny that charge. Eighteen per cent state no opinion. Only 7% of the doctors themselves reply that physicians' incomes, compared with those of their patients, are too high.

Only small numbers of people believe doctors charge higher fees to people who carry medical insurance.

Again, only 13% of the public say their own doctors charge higher fees to people with medical insurance and less than a third (31%) say most doctors do. A small percentage of doctors themselves (18%) agree that physicians hike fees for people with insurance.

Groups that are most critical of doctors' fees and incomes include lower-income people, Southerners, non-whites, people without family doctors, and those with only grade-school education.

Here is how these groups compare with the general public on five questions bearing on finances:

Think that most doctors—	*Lower income people*	*People in the South*	*Non-whites*	*No high school*	*Have no doctor*	*Total public*
Charge to much	48%	49%	47%	49%	49%	43%
Have raised fees too fast	42%	40%	43%	41%	38%	35%
Charge more to policy-holders	33%	37%	33%	34%	37%	31%
Make too much money	44%	44%	37%	42%	46%	38%
Plan to get rich quick	35%	38%	35%	38%	36%	30%

In connection with a query about doctors' charges, the public was asked, "Which, if any, do you think are most likely to charge more than they should—general doctors, surgeons, or other specialists?" Other specialists are mentioned most often (54%). Surgeons are listed by 29%, and general doctors by 3%. Six per cent say "none or equal". Most critical (60%) of the charges of other specialists are people in the Central States (general public, 54%).

The public thinks of doctors as being much better businessmen than doctors do.

Doctors are convinced that they are poor businessmen, but the public takes an almost diametrically opposite view, especially with their own family doctors. Only 13% of the doctors themselves say most doctors are good businessmen, yet two-thirds (67%) of the public say their own doctors are, and almost half (48%) say most doctors are. The people deny that most doctors are not good businessmen for these reasons: they live well and are successful (10%); they are intelligent and capable (7%); they make money (5%); their billing and business activities (5%).

Physicians say medical men are not good businessmen because they: are too busy (21%); are easy marks, avoid other business (17%); are not trained in business (16%); keep poor records and follow poor billing practices (12%); are interested only in medicine (11%); and don't think about money (4%).

The two groups with the highest agreement (23%) that most doctors are not good businessmen are people of college background and upper income people.

The public is by no means so critical of doctor bills as it is of other costs of medical care.

Of all economic aspects of medicine, physicians' charges are least criticized. Doctors' fees are thought to have risen the least since World War II in comparison with hospital and drug bills. In answer to the question, "Which part of the cost of medical care would you say has gone up in price fastest since World War II—doctor bills, hospital bills, or drug bills?", the following responses were tallied:

	Public	*Doctors*
Hospital bills	41%	71%
Drug bills	32%	24%
Doctor bills	9%	1%
No opinion	18%	4%

Almost five times as many people say hospital bills have risen the fastest as say doctors' bills have. Almost four times as many mention drug bills as having increased with the greatest speed. The fact is that hospital bills have been increasing at the sharpest rate of the three.

In each instance, people naming a specific type of bill as having risen fastest generally claim the increase has been too great. Yet doctors' fees are least criticized on this count. Only 7% of the 9% who say doctors' bills have risen with the greatest speed say the fees are higher than they should be. But 26% of the 41% who list hospital bills first say hospital charges are excessive, and 23% of the 32% who mention drug bills first claim these bills are higher than necessary.

"Do you think that hospital (drug, doctor) bills are higher than they need be or not?"

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	Public			Doctors	
	Hospital	*Drug*	*Doctor*	*Hospital*	*Drug*
Yes, higher	26%	23%	7%	25%	14%
No, not	10%	5%	1%	35%	8%
Qualified or no opinion	5%	4%	1%	11%	2%
Total	41%	32%	9%	71%	24%

Only 1% of the medical profession itself thinks that doctor bills have risen fastest; 71% of the doctors say hospital bills and 24% of the doctors say drug bills have climbed with the greatest speed. Doctors, however, are more inclined to defend than criticize increases in hospital charges. Of the 71% naming hospital charges, only about one in three (25%) think these charges are higher than they should be, and 35% say they are not. A greater percentage (14%) of doctors who say drug bills have climbed fastest (24%) say charges for these products are higher than necessary.

Both public and doctors were also given the opportunity to list their opinions as to the reasons why costs have risen so fast. The chief reasons given for the increase are for the most part not critical and practically no one blames the doctors for increases in hospital or drug bills.

People are evenly divided on the question of fixed fee scales, while doctors favour sliding scales by about 2 to 1.

For years doctors have charged in large measure according to the patient's ability to pay. In the past few years medical insurance has tended to bring about pressures for more standardization of medical costs. Yet, according to the survey, the move to establish fixed fees is not yet in demand by a majority of the public. The traditional sliding scale has practically as much support. When the pubilc was asked, "Do you think that doctors should charge the same fees to all their paying patients or that they should charge more to patients who have more money?" they reply:

Same to all	47%
More to some	46%
Qualified answers	3%
No opinion	4%

	Public			Doctors	
Reasons for increases in charges	*Hospital bills*	*Drug bills*	*Doctor bills*	*Hospital bills*	*Drug bills*
Labour costs	16%	4%	1%	47%	4%
Material, equipment costs	13%	3%	1%	33%	3%
General inflation	9%	5%	3%	12%	2%
Profiteering	3%	6%	3%	1%	3%
New drugs, research	1%	8%	*	1%	11%
Advertising expense	—	*	—	—	4%
(And miscellaneous other reasons)	*Less than ½%.				

Labour, material and equipment costs, and general inflation are blamed mainly for increased medical costs by both doctors and the public. Only small percentages of the public cite profiteering as the reasons for higher costs. This indicates that most people, though aware that medical costs have risen since World War II, are not incensed about increases and view these increases as they do increases in other living costs.

Even in those sub-population groups who might be expected to be more critical of doctors' fees, for example, little variation between opinions of the general public is seen:

A majority of people have the impression, however, that their own physician does employ a fixed fee scale. More than half (55%) say that, except for charity cases, he charges all patients the same fees, while about one in four (23%) say he does not charge the same. Twenty-two per cent have no opinion on this question.

The medical profession apparently still is inclined towards the philosophy of charging according to ability to pay. Two out of three doctors say they think doctors should charge more to some patients, while one out of three favour charging the same fee to all. Many physicians object to the wording of the ques-

Think that doctor bills—	*Lower income people*	*People in the South*	*Non-whites*	*No high school*	*No M.D.*	*Total public*
Have gone up fastest	13%	10%	11%	9%	12%	9%
Are higher than necessary	11%	8%	6%	6%	9%	7%

tion, "Do you think the doctors should charge the same fees to all their paying patients or that they should charge more to patients who have more money?", saying it should read instead, ". . . charge less to patients who have less money".

	Doctors
Same to all	32%
More to some	62%
Qualified answers	4%
No opinion	2%

The public wants cost estimates for treatment of major illnesses.

Three persons in four think their doctors should give cost estimates for the treatment of major illnesses. Most doctors say they do this, but only half the public confirms this claim. Only one person in eight (12%) thinks the cost should not be discussed in advance.

"Do you think he should tell his patients ahead of time what he thinks the cost will be?"

Public	
Yes, he should	76%
No, he shouldn't	12%
Qualified answer	8%
No opinion	4%

Three people in ten (30%) say the doctor does not prepare them in advance for the cost of treatment. Almost half (48%) say he does give them advance estimates, but about a fifth (22%) do not hazard an opinion. Three-fourths (77%) of the doctors say either that they usually tell patients about the expected cost or that they wait until asked to discuss fees.

"Do you usually tell your patients ahead of time about what the cost of treatment for major illnesses probably will be?"

Doctors	
Yes, I do	60%
Yes, if asked	17%
No, I don't	18%
Qualified answers	4%
Don't know	1%

The fact that three out of four doctors do discuss costs in advance indicates that the campaign of the American Medical Association to encourage this procedure is meeting with nationwide acceptance.

Despite publicity on the subject, only a minority of the public knows what fee-splitting is. Even though they cannot define it accurately, they disagree with the doctors' feeling that reports have overstated it.

When asked what the term "fee-splitting" meant, only 15% give correct definitions, 23% give incomplete definitions, 8% give incorrect definitions, and more than half (54%) admit they don't know what it is. Highest understanding of the term, including those giving possibly correct definitions, is found among the upper income group (63%) and the college-trained group (65%). Least understanding of the term (14%) is revealed by non-whites.

Only 11% of the public say their own doctors split fees on referrals to other doctors, but 57% give no opinion. Twenty-nine per cent say most doctors split fees on referrals, but again, more than half (51%) do not venture an opinion. Only 5% of the doctors say that most physicians split fees and 91% deny that doctors do. Evidently there is still considerable misunderstanding about the subject.

Considerable publicity has been given to the subject of fee-splitting in the past two years. Of the 38% of the public who give correct or possibly correct definitions, 17% say that it has not been exaggerated. Four out of five doctors say that it has been greatly exaggerated.

"Do you think that the amount of fee-splitting has been exaggerated to the public or not?"

	Public	*Doctors*
Yes, it has been	10%	81%
No, it has not been	17%	9%
Qualified answers	1%	3%
No opinion	10%	7%

Apparently, not everyone among either the public or the medical profession condemns fee-splitting. When asked what should be done about it, only 18% of the doctors and 8% of the public say "stop it", giving no method. Six per cent of the public and 9% of the doctors reply, "Nothing, it's necessary, all right." Medical society action or expulsion is suggested as a panacea by 15% of the doctors and 3% of the public. The same percentage of people (3%) say "leave it to doctors and their own ethics", and 5% of the doctors agree. The following courses of action also are suggested: legislate against it (public, 1%; doctors, 3%); separate fees (public, 1%; doctors, 5%); tell the patient (public, 1%; doctors, 6%); and establish an equitable fee scale (public, 1%; doctors, 9%). Eighteen per cent of the doctors give no suggestion and 11% of the public say they don't know what should be done about it.

As might be expected, the highest ratios of those who say fee-splitting has not been exaggerated to those who say it has been are found among people who do not like most doctors (5 to 1) and those who do not like the A.M.A. (3 to 1).

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In the medical profession itself, surgeons least often deny that the extent of fee-splitting has been exaggerated to the public, but they absolve most doctors of engaging in it. General practitioners most often (86%) say that reports have been over-stated.

"Do you think that the amount of fee-splitting has been exaggerated to the public or not?"

	General practitioners	*Internists*	*Surgeons*	*Other specialists*
Yes, it has been	86%	74%	64%	80%
No, it hasn't	8%	9%	14%	9%
Qualified answers	1%	5%	10%	4%
No opinion	5%	12%	12%	7%

But only 2% of the surgeons, as compared with 7% of the general practitioners and 3% of other specialists, say that "most doctors" split fees.

A somewhat related question with ethical as well as economic aspects was asked to get opinions about the practice of getting commissions on drug prescriptions. People were asked, "Does your doctor get a commission from druggists on his prescriptions?", to which only 17% say "yes" and 31% say "no". However, more than half (52%) give no opinion. Yet, when the same question was asked about most doctors, three out of ten (30%) say "yes" and only 22% say "no". Why opinion should be more solidified where most doctors are concerned is not certain, but it evidently bears out the findings of the survey that people are more inclined to accept unfavourable assumptions against doctors in general than they are about their own physicians.

No doctors say it is definitely true that most doctors get commissions from druggists and only 1% say this is probably true. Ninety-five per cent deny that doctors do get commissions on prescriptions.

Half of the public is satisfied with present insurance plans, but more doctors say insurance plans are not meeting the need.

Another question pertaining to the economic side of medicine was asked to evaluate people's opinions in regard to the adequacy of health insurance plans. Half of the people (51%) show satisfaction with present plans. But not quite half of all the doctors are satisfied that plans are adequate, since 53% say they are not filling the need. The chief need that doctors think is not being met is full population coverage, while the public is less explicit in describing any inadequacies they feel exist.

"What more is needed?" (In regard to health insurance.)

	Public	*Doctors*
Wider population coverage	6%	22%
Chronic illness coverage	3%	12%
Medical doctor, office, house call coverage	2%	9%
Drug and medicine coverage	1%	*
Coverage (other or not specified)	9%	11%
Payments too low	5%	5%
Costs too high	5%	4%
Too many loopholes, cancellations	4%	4%
Plans are abused	1%	1%
Miscellaneous mentions	5%	13%

(*less than ½%)

The highest degree of protest that existing medical and hospital insurance plans are not filling the need comes from those who dislike the A.M.A. (61%). Next highest (36%) comes from those in upper income groups and college-trained people. Doctors in the West show highest dissatisfaction with existing medical and hospital insurance plans. Five-eighths (63%) of them as compared with about half of the doctors (49%-52%) in other sections of the country say present-day insurance plans are not filling the need.

Doctors expect the public to be more critical of medical costs than they actually are.

Throughout that portion of the survey dealing with views on medical bills and medical economics, it is quite clear that physicians themselves anticipate greater criticism of medical fees than the public actually voices. Doctors' charges come in for the least amount of criticism, for only one person in ten registers disapproval. Some people may believe that doctors make too much money, but this may be partially explained by the fact that people lose sight of the long working week of the physician. The average doctor puts in at least one extra eight-hour working day each week which the average person takes as a holiday. Also, the belief that doctors make too much money, even though it is not widespread, may reflect the very human trait of envy of those who are more prosperous, whether prosperity is justified or not. Even increases in hospital and drug bills, which are considered to have risen faster than doctor bills by the public, apparently are accepted by most people as a part of the inflationary economy. The wide-spread belief that existing health insurance plans are satisfactory reflects a healthy reliance on self-management of income needs where medicine is concerned. The medical profession, which is not yet completely satisfied with today's health insurance plans, can continue to work towards development of the kind of coverages which will eventually eliminate any complaints about the economic side of medicine.

VOICE OF THE PUBLIC PRESS

"State Medicine"—Dr. D. E. Rodgers, clinical associate in medicine, University of Saskatchewan, speaking to students and faculty: "Control by government of the medical profession, research, education and practice, in a young and robust country like Canada is unthinkable, unacceptable and entirely wrong, in both the moral and social sense. In planning for the future of medical care, we must be aware of the dangers of a strongly centralized administration. We must do with our legislation in medical care as we have done with our laws—let them remain reasonable rather than strict." Dr. Rodgers agreed that a strong administration will be an important and necessary force in future medical care programs. "This challenges us to provide the best and the most enlightened administration possible," he said. *(Regina Leader-Post)*

* * *

Dr. Gordon Johnston, Vancouver, newly elected president of the British Columbia Division, C.M.A.: British Columbia doctors will oppose any national health scheme that puts control of medicine into the hands of laymen . . . "We don't feel laymen should control medical practice in Canada because they don't know anything about it." Doctors, he said, are in favour of a scheme that would maintain the fundamental principles of good doctor-patient relationships. *(The Vancouver Sun)*

* * *

Something like a national health plan is "bound to come" in Canada but it should come in stages. So said Sir Geoffrey Keynes, consulting surgeon to St. Bartholomew's Hospital, London, England, and Sims Commonwealth Travelling Professor, in an interview. "The health of a nation is so important that something like a national health plan is bound to come . . . But I should hope that in a new country like Canada it should be achieved by stages and not in the sudden precipitous way in which it was forced on to us in Great Britain . . . ," Sir Geoffrey said. *(The Vancouver Province)*

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Doctors Overworked—Dr. Renaud Lemieux, C.M.A. president, said in Victoria, B.C., that Canada's doctors are overworked and underpaid. Doctors, he said, work an average of 64 hours a week and receive no payment for 20 to 25% of their services. Canada's doctors don't make as much money as the public believes, he said, because they "just forget the old bills". Moreover, because of the hard work, doctors die at an earlier age than members of other professions, Dr. Lemieux said. *(Victoria Daily Times)*

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"The practice of medicine is a strenuous, exacting profession," says the *London Free Press*, commenting on Dr. Lemieux's statement. "It demands long hours, emergency calls, night work, and always and under all conditions that fine precision and attention to detail which conscience enforces and character provides. The Hippocratic oath which medical students take, and which virtually every medical man fulfils to the letter, makes service to the sick the primary duty, and ordains a working philosophy in which service and healing take precedence over the making of money.

"That doctors in general practise their profession in the light of these unselfish canons is generally apparent. If doctors herd us into hospitals it is in order that they may save themselves a vast amount of travel-work and have the finest laboratory and technical services at their and our disposal. No overworked man is at his best, and if Canadian doctors are seriously overworked they must work out some individual or group system to ease their labours and so make their service to mankind the more valuable."

The editorial was headed "Ease Up, Doctor—We Need You."

GENERAL PRACTICE

LE MEDECIN PRATIQUE DANS L'HOPITAL MODERNE

DANS UNE ALLOCUTION prononcée lors d'une réunion des administrateurs d'hôpitaux, le Dr Adrien Paul-Hus, Président du Chapître Provincial de Québec, College de Pratique Générale du Canada, soulignaient l'importance de la fréquentation quotidienne de l'hôpital par le médecin de famille (*L'Action Médicale, Montréal,* 32: 129, 1956). Citons quelques alinéas importants de son allocution:

"L'unité de base de notre société chrétienne a toujours été, est encore la famille, et le médecin de famille en est un membre presque nécessaire, sinon essentiel. . . . On s'imagine mal en effet une famille bien organisée, vraiment complète sans ce guide compétent, ce conseiller avisé, cet ami le médecin, toujours à sa disposition, le jour comme la nuit et toujours aussi le bienvenu. . . .

"C'est ce rôle si difficile et si important qui fait du médecin praticien la base de notre belle profession. Mais c'est aussi ce rôle si complexe qu'il a le devoir de remplir, qui lui donne un droit de cité incontestable dans nos hôpitaux."

"Comment voulez-vous en effet que le médecin praticien puisse remplir son devoir avec compétence et efficacité, si on persiste à lui refuser de suivre et de traiter ses patients à l'hôpital, avec toutes les facilités que celui-ci peut procurer en diagnostic et en thérapeutique? Comment peut-on espérer le voir conserver le prestige si nécessaire à ses fonctions, si ses patients le voient traiter en inférieur dès qu'ils sont hospitalisés? Que deviendrait par exemple la formation scientifique, le prestige du meilleur interniste, du plus grand diabétologue qui soient, si pendant cinq, diz, quinze ans, on les contraignait à pratiquer leurs spécialités exclusivement dans leurs bureaux ou au domicile de leurs patients? Chers confrères des spécialités, avez-vous déjà songé à cette perspective? Le médecin praticien n'est certainement pas un être extraordinaire, mais comme le spécialiste il est bien humaine, donc limité. Ne lui refusez donc pas ce que vous jugez indispensable aux autres, cette nourriture scientifique si précieuse à tout médecin, qui est la fréquentation quotidienne de l'hôpital. . . . Ne lui refusez pas un droit que lui donne ses devoirs et ses responsabilités. . . ."

Ensuite l'orateur parlait de l'organization des départements de pratique générale dans les hôpitaux:

"Si l'on veut maintenant préciser les privilèges des praticiens de ces départements, nous

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devons nécessairement les assujettir aux devoirs et aux responsabilités des hôpitaux eux-mêmes. Trop souvent, les médecins praticiens ont réclamé à tort, non seulement le privilège de traiter leurs patients dans les départements privés des hôpitaux au même titre que le personnel médical de ses hôpitaux, mais aussi l'entière liberté de les traiter à leur guise. Ce serait là une pratique dangereuse que l'hôpital a le droit, même le devoir de condamner. Ce droit de l'hôpital est incontestable, car il découle directement de ses devoirs et de ses responsabilités envers le patient . . . , même en département privé.

"Il s'ensuit donc logiquement que l'hôpital, en acceptant un médecin praticien comme membre actif d'un département de pratique général, n'est aucunement obligé de faire dépendre ce privilège des diverses certifications que ce médecin peut présenter. Le standard de compétence requis est son affaire. On suggère cependant que ces médecins soient encouragés à faire partie du Collège de Pratique Générale du Canada, justement parce que ce Collège exige de ses membres un standard beaucoup plus élevé que la moyenne, et les oblige à un programme d'études continu, à un minimum de 50 heures de cours post-universitaires, par année. Tous les privilèges qu'auront ces médecins de traiter leurs patients publics ou privés, dans les départements de médecine, de pédiatrie ou d'obstétrique, devront être limités par leur expérience, leur jugement, leur compétence telle qu'évaluée par le Comité de Créances de cet hôpital. Si certains de ces médecins, par leurs efforts, leur travail et leurs études se rendent dignes de privilèges plus étendus, l'hôpital devrait les leur accorder, quand ce ne serait que pour créer un stimulant salutaire pour tous les autres membres de ce service de pratique générale."

Le Dr Paul-Hus affirma que les divisions intestines de notre professions contribuaient à la baisse de notre prestige et entraineraient fatalement la Médecine d'Etat.

Il dit, "S'il est vrai que la division la plus triste qui existe dans notre profession est bien celle qui sépare le médecin praticien du médecin spécialiste, il est non moins vrai que le trait d'union, seul capable de les rapprocher, de les réunir et de les unir, c'est bien plus l'hôpital que toute autre association médicale, voire même le collège des médecins. C'est là que le patient, cet ami commun, unira ces deux médecins dans un but commun, sa guérison. C'est là, que grâce à cette communion d'efforts, à ce commerce journalier et familier entre spécialistes et praticiens, les barrières fâcheuses tomberont pour engendrer une compréhension réciproque, des amitiés où la désunion n'aura plus de prise."

Enfin, il parlait de la charité humaine: "En faisant une place égale à ce médecin, on n'entravera en rien le haut niveau scientifique des soins médicaux des hôpitaux, mais on leur ajoutera une saveur qui nous fera penser à la charité d'un abbé Pierre ou d'un Dr Schweitzer."

[*We regret to record the death, on November 3, of Dr. Paul-Hus. An obituary notice will appear in the issue of December 15.*—ED.]

THE PAINFUL HIP*

ALEXANDER GIBSON, F.R.C.S.(Eng.),†
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THE HIP-JOINT is so deeply seated that it is difficult to examine directly. It has such a wide range of movement that it has to be controlled by many muscles. It has to carry not only the weight of the trunk and upper limbs but also other weights that the subject may choose to raise or to carry. The muscles must therefore be massive and powerful. Close to the joint there lie the great vessels and nerves passing to the lower limb. The fibrous structures in its vicinity are among the strongest in the body. The tasks imposed upon the joint call for a combination of strength and mobility to which in the majority of cases it responds well. In the event of incomplete response there are four indicators that all is not well. These are:

1. Pain.
2. Instability.
3. Loss of movement.
4. Shortening (actual or functional).

Instability may be ignored or compensated. Loss of movement may be of relatively little importance; shortening is usually betrayed by a limp if the discrepancy in length is marked; if small in amount its presence may not be recognized at all. Pain, however, is insistent. It interferes with activity, and breaks in upon sleep. It refuses to be ignored. There are many sources from which pain may come. Anatomically, the shape of the bones may be at fault. The muscular equipment may be the seat of fibrositis. The fatty covering may develop painful fatty nodules, probably herniated through gaps in the areolar tissue, while structures situated at a distance, e.g., an intervertebral disc or a large blood vessel, may cause pain indirectly. A classification of the causes of pain is not easy to formulate. I have attempted to

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*Lecture given at the Refresher Course, St. Boniface Hospital, St. Boniface, Man., March 28, 1956.
†This paper was presented by the author on the day before his death. It is reproduced in tribute to the memory of a great teacher. Communications about the paper may be addressed to Dr. W. B. MacKinnon, 661 Broadway Ave., Winnipeg.

group the causes in a scheme which, though not strictly logical, may have some clinical value. These are arranged under five headings: (1) disorders of growth, (2) disease, (3) degeneration, (4) trauma, (5) new growth.

1. Disorders of Growth

These manifest themselves mainly during the years of childhood and adolescence:

(a) *Coxa plana or Legg-Perthes disease.*—The general features of this are well known and will not be elaborated. In a sentence, the radiological characteristics are more impressive than the clinical ones, although this is not always so. It is not always easy to differentiate between this condition and tuberculosis.

(b) *Slipped epiphysis.*—This condition usually shows itself in early adolescence. Perhaps the radiographic appearances are the most trustworthy guide. A rapid clinical test may provide a clue. Turn the patient on his face, and flex the knee fully. Normally the heel should come to the buttock of the same side. If the heel points to the buttocks of the opposite side, this indicates diminished internal rotation, and suggests the probability of an early slipped epiphysis. The sooner the condition is recognized the better.

(c) *Coxa vara*: congenital or acquired; not considered in this paper.

(d) *Inadequate acetabular roof.*—This deficiency should be detected if possible during the first year of life. A routine check by radiography at the age of six months would lead to its discovery, and appropriate treatment could be begun.

(e) *Old reduced congenital dislocation of the hip.*—The unreduced congenital dislocation of the hip is not as a rule a source of pain or of much disability even in the presence of marked limp. It is commonly held that this condition is a cause of low back pain in later life. This is not necessarily correct. On the other hand, if the dislocation has been reduced and held for long in plaster, the effect on development of the head of the femur may be disastrous. During adolescence this is not much in evidence, but later in life osteoarthritic changes are sure to develop. The problem of congenital dislocation of the hip is cosmetic rather than functional. Its solution lies in recognition and treatment during the first 12 months of extrauterine life.

2. Disease

(a) *Acute infective arthritis.*—This may be transient in children. Often one hardly knows whether it is the result of infection or trauma. In other cases it may be severe and serious. It may be accompanied by pus formation. It is a notable fact that a joint may harbour pus for a short time without the hyaline cartilage being notably damaged. If the pus be retained, the function of the joint is likely to be permanently impaired. With the use of antibiotics one is apt to forget a cardinal principle of the old surgery, "Where there is pus, let it out." The following case illustrates the point.

B.B. was admitted to hospital with the diagnosis of poliomyelitis. Later, it was established that the condition was osteomyelitis of the neck of the femur. Considerable amounts of penicillin were given, the condition settled down, and the child returned home. The next development was a fracture across the neck of the femur. Healing was exceedingly slow. Apparently the reparative process was largely inhibited. The net result is a hip-joint with a fair amount of movement, but there is shortening of almost two inches (5 cm.).

(b) *Chronic infective arthritis.*—Tuberculosis is the chief exemplar of this. It is not a common condition nowadays except among Indians and Eskimos. One has, however, to be on the lookout for it even in unexpected places, notably among the elderly. The disease may affect the great trochanter, in which case it does not customarily invade the hip-joint although it may do so. Tuberculosis of the great trochanter may be very chronic, but it is usually amenable to adequate surgical treatment. When tuberculosis affects the hip-joint itself, there is but one cure—bony ankylosis. This is usually accomplished by surgery.

(c) *Atrophic arthritis.*—This is usually part of a generalized involvement.

(d) *Marie-Strümpell disease.*—This insidious malady is usually well established in the vertebral column before the hip-joints are affected. When the condition is bilateral, as it usually is, the pain may be severe and the disability pronounced. X-ray treatment may help, but we do not exactly know why.

(e) *The Charcot joint.*—While the condition is very disabling, pain is not a prominent feature.

(f) *Osteochondritis dissecans; osteochondromatosis.*—Perhaps these two conditions should not be lumped together. Pathologically they are of different origin. They have in common the fact that both may lead to the presence of loose bodies in the joint.

(g) *Arterial thrombosis.*—This condition is probably much more common than is generally recognized. It is characterized by pain of the claudication type on walking. In elderly people who complain of pain in the hip or buttock, the condition of the femoral artery should always be noted.

3. Degeneration

(a) *Fatty herniæ.*—These may appear suddenly; if recognized, they can sometimes be replaced with immediate relief to the patient. They are found chiefly in the neighbourhood of the posterior superior spine of the ilium.

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(b) *Calcification in tendons.*—Quite often this condition can be noted in tendons about the hip-joint: the gluteus medius, the ilio-psoas, the pyriformis. Analogy with the shoulder is obvious. It follows also that there are many cases where the tendon is damaged although no calcification is present. The term "gluteal bursitis" probably corresponds to the term "subacromial bursitis".

(c) *Ilio-psoas bursitis.*—This may be hard to diagnose. The ilio-psoas bursa commonly communicates with the hip-joint. In many cases the lesion is an extension from a hip-joint in which degenerative changes are present. The analogy here is with the "Baker's cyst" of the knee or the synovial cyst in front of the shoulder.

(d) *Osteoarthritis.*—This very common condition has recently been the subject of intensive study and experiment stimulated largely by attempts to improve by surgery the pain from which the patient suffers. It is too large a subject for the present discussion.

(e) *Irradiation necrosis.*—Two cases of this have been observed. One patient sustained a fracture of the neck of the femur after deep x-ray treatment. The fracture healed without special treatment. The other, after irradiation of a malignant testis tumour, developed necrosis of the head of the femur in the region presumably served by the artery of the ligamentum teres. At operation this portion of the head of the femur was a spongy mass of rubbery consistency.

4. TRAUMA

(a) *Gunshot wounds.*—These may be sustained in civil life as well as in warfare. There is no set pattern for them and the injuries to soft parts are frequently more important than the injuries to bone.

(b) *Fractures.*—These are usually grouped regionally as fractures of the: (i) head, (ii) neck, (iii) intertrochanteric region, (iv) acetabulum. (Pelvic fractures will not be considered.) In old age, the violence required to produce a fracture may be minimal. A special type is the "dashboard" fracture. This can usually be reduced fairly readily by traction or open operation. Almost invariably, however, the immediate result is not the permanent one. Degenerative changes in the hip-joint are almost inevitable.

(c) *Dislocation with or without fracture.*—Considerable violence is usually necessary to produce dislocation. Reduction of the dislocation may tax one's skill and energy. Degenerative changes are very apt to make their appearance at a later date.

5. NEW GROWTH

(a) *Villo-nodular synovitis.*—This is a rare condition. The term was introduced by Jaffe and Lichtenstein in 1941. It is a xanthomatous lesion of the synovial membrane and may spread to adjoining bursæ. There may be areas of rarefaction in the rim of the acetabulum and in the head of the femur. Pain may be absent. The condition may extend retroperitoneally. It is generally felt that "synovectomy with excision of the existing lesions is the treatment of choice, and that recurrences may be treated by roentgen therapy".

(b) *Osteoid osteoma.*—This interesting lesion may be found in any bone of the body, including those forming the hip-joint. The pain may be quite severe, and for some obscure reason it is much lessened by the use of acetylsalicyclic acid. Excision of the affected area commonly results in complete cure.

(c) *Osteosarcoma* (or other malignant bone condition).—This is always serious, calling for one of the most trying operations in surgery, the "hind-quarter amputation" or, less accurately, hemipelvectomy. It does not fall to the lot of many surgeons to perform many of these operations in a lifetime; a personal note from the foremost exponent of the procedure informs me that he has now done a "hind-quarter" amputation 87 times. Drastic as this procedure is, it is unfortunately adopted too late, so that although the immediate result may minister hope, the sequel is as a rule disappointing.

MANAGEMENT

With such a variety of causes of painful hip, it must be evident that management of the condition must depend upon the individual cause. It is possible, however, to group the procedures available into two main categories—conservative and surgical.

CONSERVATIVE

1. *Rest.*—In all acute conditions this is imperative. In the more chronic, particularly in osteoarthritis, it is important for the patient to find out his limits of exertion and to stay within them. If this be done, the pain in the joint may subside and allow a reasonable amount of activity for years. Sometimes it is necessary to do more than prescribe rest in bed; in such cases splinting by plaster-of-paris or otherwise may be necessary. In nontuberculous cases, it is equally important to insist on active exercise.

2. *Reduction of deformity.*—This measure may be called for in tuberculosis as a preliminary to fusion, or in other forms of arthritis where the hips have been permitted to become flexed and adducted. Anæsthesia should rarely if ever be employed. Traction, gradually increased, will often restore the desired alignment. Continuous traction, however, is apt to be not only irksome but actually painful; on this account it is preferable to use a series of plasters applied 10 to 14 days apart. These should be put on without

anæsthesia at the limit the joint will take without undue stretching of the soft parts; the improvement in flexibility is usually very gratifying.

3. *Drugs.*—The last 20 years have furnished us with many therapeutic resources beyond those possessed by our predecessors. The antibiotics (penicillin, etc.) have accomplished wonders. Let us bear in mind, however, that they have aided, not supplanted, established surgical principles. It is well to remember that their use in excess may have effects of which, after our brief experience, we are only dimly if at all aware. The antibiotics are powerful weapons; they should not be used wastefully.

Of almost equal importance in the field of tuberculosis is the introduction of streptomycin, para-aminosalicylic acid, and isoniazid. At Brandon Sanatorium it is the usual practice to give:

Streptomycin, g. 1 every 3 days intravenously
PAS, g. 10 every day by mouth
INH, mg. 300 every day by mouth.

According to Johnson and Sutter, "Two important facts are apparent. First, the fairly rapid development of resistant strains of tubercle bacilli to these agents when used alone, and contraposed to this, the delayed development of resistant strains when these agents are used in combination. Second, prolonged, continuous chemotherapy assures greater therapeutic response than short or interrupted courses of therapy."

In arthritic cases, osteoarthritis as well as the atrophic type, relief from pain is frequently obtained by injection of cortisone or one of its congeners. The relief is temporary; no lasting effects on the pathological process are to be looked for, but the respite from pain, even if only temporary, is of much value. There are indications that new chemical products are likely to appear, the effects of which will prolong the period of relief.

4. *Physiotherapy.*—Under this caption may be included such things as massage, various forms of bath, diathermy, ionization, analgesic x-rays and occupational therapy. As ancillary measures, all of them have a place.

SURGICAL

1. *The approach to the hip-joint.*—Briefly there are three aspects from which the joint may be explored: anterior, associated with the names of Sprengel and Smith-Petersen; lateral, originated by Ollier—in this approach the great trochanter with its attached muscles is chiselled through at its base, and turned upwards along with the muscle attachments; and posterior attack, developed by Langenbeck and extended by Kocher. A modification of Kocher's approach is perhaps the most widely employed today.

2. *Operative measures:* (a) *Nailing.*—This is perhaps the simplest of all hip-joint surgery. It has now superseded the plaster spica employed by Whitman in the treatment of fracture of the neck of the femur. The addition of a plate to the nail has given control of the intertrochanteric fracture. Even if the head should not unite, the use of a nail permits the patient to be out of bed in a few days. Age, of itself, lays no ban on surgical interference. Van deMark recently reported a series of 28 consecutive operations in 24 patients between the ages of 90 and 99 with a mortality of 14.28%. His conclusion is that "Hip nailing is definitely indicated in the old patient who is mentally alert, co-operative and in good health . . . The procedure is contraindicated in patients who are unco-operative, or seriously ill with systemic disease."

(b) *Excision.*—This is called for in cases of tuberculosis affecting the great trochanter. It is still employed as a preliminary step in the Colonna operation or the Milch-Batchelor osteotomy. Implantation of the stump of the great trochanter into the acetabulum may give a hip that proves satisfactory for years. Ultimately it is apt to dislocate from under the acetabular roof, causing a certain amount of instability and pain.

(c) *Arthrodesis.*—Many patients with bony ankylosis of the hip-joint go through life with no pain and with negligible disability. From the surgical point of view, bony ankylosis is not always easily obtained, almost certainly because with plaster splinting fixation is imperfect. The means applied to aid in fixation are many and varied. There is the long nail of Watson-Jones, the iliac grafts by Albee, Hibbs, or Ghormley, the ischio-femoral arthrodesis of Brittain or that of Trumble. Charnley has employed a central dislocation of the head and Abbott has used a wide abduction implantation followed by osteotomy later to restore parallelism of the lower limbs.

(d) *Arthroplasty.*—If freedom from pain can be achieved along with stability, then every particle of mobility at the hip-joint is clean gain. Many plans are adopted to bring this about. The vitallium cup or cap has a reasonably successful record over a period of years. More fashionable of late is the use of a prosthesis. This measure was introduced by the brothers Judet. Since then a host of varieties of shape and material have made their appearance. The ideal arthroplasty has not yet been devised.

(e) *Osteotomy.*—In many quarters it is recognized that reconstitution of a hip-joint can never be an operation of precision. In the osteoarthritic joint the soft parts as well as the bones are far from normal. Osteotomy of the shaft of the femur high up, combined with medial displacement of the shaft of the bone, can provide a stable, painless hip with a remarkably good range of motion. One disadvantage of this operation used to be that a long spell in plaster

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was necessary before union of the separated fragments could occur. Of recent years different forms of "splines" and plates have been devised to hold the fragments immobile. By means of these devices the long period of immobility of the patient is no longer requisite. In this country, the name of McMurray is linked with this form of osteotomy. When a patient has bilateral ankylosis of the hip-joints, as in Marie-Strümpell disease, his plight is a sorry one. It may be mitigated by use of the Milch-Batchelor technique of angular osteotomy.

SUMMARY AND CONCLUSIONS

1. Pain in and about the hip is a common finding at all ages.
2. Pain may result from relatively unimportant causes, or it may indicate a very grave outlook.
3. Many cases of painful hip are amenable to conservative treatment; others require surgery.
4. In spite of its deep location, the hip-joint itself is readily accessible.
5. The painful hip may be ameliorated by appropriate surgical treatment e.g., by arthrodesis, by arthroplasty, or by osteotomy.
6. Many aspects of the problem of the painful hip still await a satisfactory solution.

COLLEGE OF GENERAL PRACTICE OF CANADA

HOSPITALS WITH GENERAL PRACTICE RESIDENCIES

JULY 1957

Alberta.—St. Michael's General Hospital, 13th St. and 9th Avenue S., Lethbridge. Sister M. Consolata, Administrator.

British Columbia.—Royal Jubilee Hospital, Victoria, B.C. Dr. J. L. Murray Anderson, Medical Administrator. St. Joseph's Hospital, Victoria, B.C. Dr. A. J. Brunet, Medical Superintendent.

Manitoba.—St. Boniface Hospital, St. Boniface. Dr. Paul L'Heureux, Medical Director. Victoria Hospital, Winnipeg. Mrs. V. West, Superintendent.

New Brunswick.—Saint John General Hospital, Saint John, N.B. Dr. Carl R. Trask, Director.

Nova Scotia.—Aberdeen Hospital Commission, New Glasgow, N.S. Dr. H. C. McKay, Medical Superintendent.

Ontario.—Belleville General Hospital, Belleville. Kenneth E. Box, Administrator. Hôtel-Dieu Hospital, Cornwall. Sister St. M. Magdalen, Administrator. Ottawa General Hospital, Bruyere Street, Ottawa. Dr. J. Paul Laplante, Medical Director. The General Hospital of Port Arthur, Port Arthur. J. A. McNab, Administrator. St. Thomas-Elgin General Hospital, St. Thomas. Bertram G. Thacker, Administrator. St. Joseph's Hospital, Sarnia. Sister M. St. Paul, Superintendent. New Mount Sinai Hospital, 550 University Avenue, Toronto. Sydney Liswood, Administrator. St. Joseph's Hospital, Toronto. Sister M. Estelle, Superintendent.

Quebec.—Hôpital Notre-Dame, Montreal 24, Quebec. Dr. J. R. Boutin, Medical Director. Montreal General Hospital, Montreal. Dr. William Storrar, Medical Director. Royal Victoria Hospital, Montreal. Dr. Ronald V. Christie, Physician-in-Chief. L'Hôtel-Dieu de Québec, Québec. Dr. J. B. Jobin, Medical Director. Hôpital St-Joseph, 779 Ste.-Julie, Trois-Rivières. Dr. J. J. Laurier, Medical Director.

Saskatchewan.—St. Paul's Hospital, Saskatoon. Sister A. Lachance, Administrator.

Association Notes

CANADIAN JOURNAL OF SURGERY

Surgeons across Canada will be glad to know that at last Canadian surgery is to have a journal of its own. No longer will it be necessary to search through a dozen different journals in the United States and elsewhere to obtain a conspectus of the surgical movement in Canada. It is hoped that on October 1, 1957, the first number of a quarterly journal, published by the Canadian Medical Association, under the direction of a distinguished surgical board, will appear. Directly after the Royal College of Physicians and Surgeons meeting in Toronto, the new Editorial Board of this Journal held its first meeting at C.M.A. House, on Sunday morning, October 28, 1956. At this meeting the chairmanship of the Board was placed in the hands of Dr. R. M. Janes, Professor of Surgery in the University of Toronto and a President of the Royal College of Physicians and Surgeons of Canada. The remainder of the Board was constituted by the heads of departments of surgery in Canadian medical schools. It was agreed, in addition, to invite organized groups representing specialties in surgery to appoint each a member to serve on an advisory board in such subjects as gynæcology, neurosurgery, otolaryngology, orthopædics, plastic surgery, urology, ophthalmology, thoracic surgery and anæsthesia. Thus all who profess and call themselves surgeons may feel that they have some stake in this new venture. It is also agreed that publication should be in either of the two official languages of Canada, and that summaries in the other language be freely used.

The new Journal will carry original articles, review articles, editorials, news items, and special features. Although the Canadian Medical Association has set aside a sum of money to promote this Journal and to launch it, for it will undoubtedly be some time before the publication is self-supporting, the support of every surgeon in Canada is essential. This Journal will stand or fall by the support it is given by those for whom it is primarily intended, namely the surgeons of Canada. In the near future, a signed letter will go out, not only to the surgeons, but also to the many practitioners in Canada who include in their practice a certain amount of surgery, inviting them to subscribe to this new Journal and thus assure its success. The names of the Editorial Board are a guarantee to potential subscribers that they will not be wasting their money, and that the Journal is no ill-conceived attempt, but will be truly worthy of Canadian surgery at the present time.

MEDICAL SOCIETIES

CANADIAN ASSOCIATION OF ANATOMISTS

Anatomists from ten of Canada's medical schools met on Wednesday, October 17, at the University of Montreal and formed a Canadian Association of Anatomists. Objectives and procedures were formulated in a Constitution and a Council of twelve members was elected. The following officers were chosen for the first year: Honorary President, Professor J. C. B. Grant, University of Toronto; President, Professor A. Skinner, University of Western Ontario; 1st Vice-President, Professor I. M. Thompson, University of Manitoba; 2nd Vice-President, Dr. L. Poirier, University of Montreal; Secretary, Professor J. Auer, University of Ottawa; and Treasurer, Professor D. C. Matheson, Queen's University.

The other members of Council are: Professor H. E. Rawlinson, University of Alberta, Professor P. Jobin, Laval University, Professor C. P. Martin, McGill University, Professor R. L. de C. H. Saunders, Dalhousie University, Professor S. M. Friedman, University of British Columbia, Dr. S. Bensley, University of Toronto, and Dr. Y. Clermont, McGill University.

The purpose of the new Association is to advance the science of anatomy in Canada; to hold an annual meeting for the presentation of scientific papers; and to co-operate with other scientific bodies in the development of scientific programs in Canada.

Preliminary work of an exploratory nature has been done for the past year by an interim committee composed of representatives from each of the medical schools of Canada.

While the Association has been formed primarily by anatomists from the various medical schools it is not the intention to confine membership to these, but to include any persons who have made contributions to this science, as well as to offer associate membership to persons who have a positive interest in anatomy and who wish to attend the meetings.

PHARMACOLOGICAL SOCIETY OF CANADA

We welcome as the newest addition to the specialist societies of Canada the Pharmacological Society of Canada, which was founded on October 17, 1956. Its President is Dr. Eldon M. Boyd, Head of the Department of Pharmacology at Queen's University, Kingston, Ontario, and its Vice-President Dr. K. I. Melville of McGill. Others on the first standing committee are Drs. W. Kalow (Secretary-Treasurer), J. G. Aldous, M. G. Allmark and M. Nickerson.

The organization of this society was first discussed in October 1954, when 21 pharmacologists convened at Hart House, University of Toronto, at the invitation of Dr. J. K. W. Ferguson, who headed the organizing committee and lectured at that time. Further meetings were held in the University of Western Ontario in October 1955 and at McGill University in October 1956, with interim meetings in San Francisco and Atlantic City. The meetings were made to serve a dual purpose, since they included a series of symposia upon such subjects as graduate training in pharmacology, undergraduate teaching of pharmacology and assessment of drug toxicity.

The new society will act in affiliation with the Canadian Physiological Society, and has as its object the promotion of the science of pharmacology in its widest sense. Any person who has conducted research and published papers in pharmacology or engaged in teaching of the subject is eligible for membership. The Society plans to hold annual meetings, together with such additional meetings as the standing committee shall determine. It has been indicated that the Pharmacological Society of Canada is prepared to consider rendering to organized medicine in Canada any service of which it may be capable in the field of therapy. Dr. Eldon Boyd would appreciate receiving applications and supporting documents from any member of the Canadian Medical Association for charter membership in this society.

CORRESPONDENCE

ANÆSTHESIA PREMEDICATION

To the Editor:

I must apologize for prolonging this discussion, but the subject is of such tremendous importance to the well-being of our patients that I feel that I must enter this controversy.

Dr. Shields has rightly stated (Oct. 15, p. 693) that "there appears little justification for routine preoperative use of tranquillizing drugs such as Largactil". It is on this topic that I wish to say a few words. It seems to be much too little realized that these agents are potentially exceedingly hazardous because of their marked potentiating effect upon anæsthetic agents, effect on the cardiovascular system, etc. Unless the indication for their use is clear-cut and the use of tranquillizing agents promises to be of real advantage to a particular patient (an infrequent event indeed!), their use in preoperative medication is *not* justified. Even in places where trained anæsthetists are not available it has become a routine to use drugs such as Largactil for preoperative medication. If many experienced anæsthetists consider them too hazardous for routine use, how much more dangerous must be their promiscuous use by untrained or semi-trained anæsthetists. I know and have heard of a number of fatalities and near-fatalities which have resulted from the misuse of these agents, accidents which were entirely unnecessary and would probably not have occurred had more conventional and safer medication been employed.

I would like to make a passionate plea, Sir, for the tranquillizers to be reserved for those cases where a real benefit to the patient accrues and then only in the hands of the trained anæsthetist.

GORDON M. WYANT, F.F.A.R.C.S.,
Professor of Anæsthesia.
Department of Anæsthesia,
University of Saskatchewan,
Saskatoon, Sask.,
October 23, 1956.

THE BLOOD-BRAIN BARRIER

To the Editor:

I read with interest and a certain amount of amusement the review of Dr. Bakay's book, "The Blood-Brain Barrier", which appeared in No. 7, Vol. 75, of the *Canadian Medical Association Journal*. Certainly arguments could be found against including in a book review expression of personal emotions and biased personal opinions, though on the other hand that type of review adds sparkle to an otherwise dry scientific text. However, the purpose of this letter is not to discuss the matter of the form of the review, but rather to point out an error which should not have been allowed to appear.

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The review implies that the term "blood-brain barrier" has been invented or introduced by Dr. Bakay. As is known to everybody familiar with the subject, this implication is wrong. The term has been used for about 30 years, and its introduction seemed to be justified by the fact that the selective permeability of the cerebral blood vessels is different from that of other organs in many important aspects. Because of its brevity and descriptiveness, it acquired a permanence in medical terminology without obscuring the complexity of problems hidden under the simple term.

J. OLSZEWSKI, M.D.

Department of Pathology,
University of Saskatchewan,
Saskatoon, Sask.,
October 15, 1956.

[Our reviewer writes:

"Any implication that Dr. Bakay had invented the term blood-brain barrier was not intended and if that is the error to which your correspondent refers I gladly take the opportunity to correct a wrong impression that the review gave him. The phrase has, however, been growing in popularity in recent years, partly due to the prominence that Dr. Bakay has given it. But if his quarrel is with the derision with which I view the term, then I am glad to take issue with him. It may be a losing battle because the cliché is now so thoroughly respectable that it is accepted uncritically. It is because it *does* obscure the complexity of underlying problems that its use is objectionable. Every organ has its barrier between the blood and the parenchyma; the complexities of each "barrier" are peculiar to the organ and the brain is unique only in the nature of its "barrier", not in its possession of one. To be consistent, therefore, we should also talk about the blood-pancreas barrier, the blood-tooth barrier and so on throughout the body, which is surely rather absurd. Further, the expression infers that there is a mechanism that holds up the one-way passage of substances from the blood to brain, which is at best only half the story; it would be as justifiable to call it the brain-blood barrier. The term is certainly brief but it can hardly be called descriptive. The use of it, however, is a successful attempt to introduce sparkle into what should be dry and scientific. Nevertheless, as the review stated, those who are interested in ionic exchange between blood and tissues, particularly brain, should read this book.]

SPECIAL CORRESPONDENCE

The London Letter

(From our own correspondent)

THE COST OF HEALTH

The Minister of Health's annual report for 1955 shows that the cost of the National Health Service in England and Wales was £495 million—an increase of £22 million over the previous year. A point brought out by the Minister, to which he draws attention every year but which does not yet appear to be appreciated by the populace at large, is that contributions from the National Insurance Fund covered only one-fourteenth of the gross cost of the Service. This is equivalent to 10d. out of each weekly total contribution for men into the National Insurance Fund—a small fraction of the full weekly contribution paid by, or in respect of, each person. By far the greatest part of the expenditure on the Service—£388 million—is met by the Exchequer out of moneys voted by Parliament. The remainder is largely made up by payments by patients: £6 million paid by patients for drugs and appliances (made up of the shilling which has to be paid by patients on each prescription form dispensed for them under the Service), £7 million paid by patients for dental treatment and dentures, and £5 million paid by patients for spectacles.

Equally illuminating are the figures furnished in the annual report of the Ministry of Pensions and National Insurance for 1955. These show that the combined cost of social benefits paid by the Ministry totalled £850 million. New claims for sickness benefit accounted for £84½ million, whilst maternity grants and allowances came to £13 million.

PAYING FOR PRESCRIPTIONS

The vicious impact of politics on medicine in a State Medical Service is well exemplified by the raucous reaction of the Socialist Opposition in Parliament to the Chancellor of the Exchequer's announcement that, as from December 1, he proposes to change the method of charging for National Health Service prescriptions from 1s. per form to 1s. per item. This is what most people consider a laudable attempt on the part of the Chancellor to slow up the steadily rising cost of prescriptions to the Exchequer. It is estimated that it will bring in an additional £5 million a year. As the average cost per prescription is now 5s., and as each prescription form contains an average of 1¾ items, the new arrangement will mean that the patient will be expected to contribute 2s. towards the 8s.3d. which each prescription form costs. As *The Times* cogently asks: "If the public could afford a shilling for a prescription in 1949, as the Government then held, could it not afford somewhat more in 1957?" The British Medical Association has expressed the view that "doctors will be concerned about the medical repercussions of this decision" and describes it as "discriminating unfairly between different classes of patients".

THE POSTGRADUATE MEDICAL SCHOOL

The Postgraduate Medical School of London is celebrating its coming of age by appealing for £750,000 to cover the cost of the extensive expansion program which it is about to undertake. The position has now been reached that the School is unable to cope with the present number of students—far less accept the increasing number of applicants who wish to join the School every year—until it has more accommodation, both for teaching and for research. Unlike the older academic institutions in the country, the School has neither endowments nor subscribers, and is almost entirely dependent for its income upon a University grant of around £200,000 a year. This sum is practically all required for current expenditure and leaves nothing for capital expenditure—certainly not on the scale now necessary. It is to obtain the money for this essential new building that the appeal has been launched.

The School can rightly claim to be the first organized University School in this country to be devoted entirely to the further education of graduates in medicine. In its first 20 years, over 12,000 graduates have passed through its hands, 1,306 of whom, it is interesting to note, came from Canada.

RADIOACTIVE CÆSIUM

The Royal Marsden Hospital has just received its first allocation of radioactive cæsium produced from radioactive waste. This has come from the fission products of the atomic piles at Windscale, Cumberland. According to the United Kingdom Atomic Energy Authority, no other country has a production plant designed to produce regular supplies of radioactive cæsium. It is planned to produce radioactive cæsium on a large scale for use in appropriately equipped hospitals throughout the country.

WILLIAM A. R. THOMSON

London, November 1956.

ABSTRACTS *from current literature*

MEDICINE

Salicylate Ingestion: A Frequent Cause of Gastric Hemorrhage.

J. J. KELLY, JR.: *Am. J. M. Sc.*, 232: 119, 1956.

A group of patients are reported who gave evidence of upper gastrointestinal hæmorrhage after the ingestion of salicylates. These subjects were similar in that bleeding was painless, free acid was found in the fasting stomach, and no roentgenographic proof of an ulcer was present. Three patients experienced numerous bouts of melæna over many years, always preceded by aspirin ingestion. Hypoprothrombinæmia was not the cause of the bleeding, as the prothrombin times were normal in all cases where it was determined and the amount of salicylates taken was inadequate to depress significantly the prothrombin concentration of the blood. Gastric allergy to salicylate may have been responsible for the bleeding in the cases where hæmorrhage was frequent over a long period.

The use of salicylates appears to increase the frequency of bleeding in patients with proven peptic ulcers. The mechanism of bleeding both in the patients with proven peptic ulcer and in the other group without symptoms or laboratory evidence of peptic ulcer is not clear. A local mucosal factor may be the cause, but it seems more likely that aspirin, by augmenting the gastric acidity, leads to peptic erosion and bleeding. The hypothesis is advanced that seasonal incidence of peptic ulcer activation may be partially explained by the more frequent use of this drug in the "ulcer months".

All patients with upper gastrointestinal hæmorrhage should be questioned concerning the use of salicylates or proprietary drugs containing salicylates. This may be a lifesaving measure. S. J. SHANE

Heart Failure and Lung Disease.

H. H. HECHT: *Circulation*, 14: 265, 1956.

The confusing and complex interplay of factors leading to "cor pulmonale" may be somewhat clarified if the effects of excessive pulmonary hypertension causing right heart overloading ("pulmonary hypertensive heart disease") are separated from the ventilatory defects that result in arterial desaturation, erythrocytosis, and moderate pulmonary hypertension ("emphysema heart"). In the former group, heart failure dominates the clinical picture; in the latter, it is assumed that heart failure occurs on the basis of a "myocardial factor"—presumably arteriosclerotic heart disease—whose manifestations are coloured and modified by the coexisting and contributing respiratory dysfunction. These two distinct forms frequently overlap, and pulmonary hypertension may be severe enough to be the chief precipitating cause of failure in emphysema, particularly in young subjects and in patients with kyphoscoliosis. Respiratory disturbances, fibrosis, and loss of pulmonary elasticity may accompany heart failure secondary to right ventricular overloading which may ultimately lead to significant arterial desaturation at rest and the development of polycythæmia, even in this group. It is typical, however, that the disturbances leading to cor pulmonale rarely, if ever, involve the actual pulmonary function of alveolar-capillary gas exchange; they are confined to the abnormalities of the pre-capillary pulmonary vasculature and to the mechanical apparatus of the chest cage and of the pulmonary parenchyma concerned with breathing mechanisms.

Pulmonary hypertensive heart disease, whatever its cause, has a monotonous symptomatology dominated by signs of heart failure. In cor pulmonale due to emphysema and its allied types, the clinical picture is varied, and oxygen deficiency with arterial desaturation is of central significance, raises pulmonary artery pressure by a mechanism not fully understood, and stimulates erythropoiesis. When erythrocytosis has occurred, heart failure from cor pulmonale will soon make its appearance. Unless the arterial oxygen content falls sharply on exercise, resting oxygen saturation values in excess of 80% do not cause this type of polycythæmia; nor does polycythæmia as such, as in erythræmia ("vera"), result in significant arterial desaturation, pulmonary hypertension, or heart failure. However, little is known concerning the hæmodynamic load imposed by an increase in blood viscosity.

The management of cor pulmonale must recognize the multiplicity of factors concerned and weigh their relative significance in any given subject. The kaleidoscopic appearance of cor pulmonale requires flexibility of therapy based on a grasp of the individual pathophysiologic interrelations, which may differ from patient to patient. S. J. SHANE

SURGERY

Effect of Rubber Tubes on the Healing of Anastomoses of the Common Bile Duct.

S. WILLIAM *et al.*: *A.M.A. Arch. Surg.*, 72: 908, 1956.

Experimental work on dogs in which, following a period of ligation-occlusion of the common duct, the latter was transected and resutured, showed that the presence of a limb of the T-tube drain did not result in stenosis of the duct. No significant inflammatory reaction which could be blamed on the T-tube rubber was demonstrated, though in some of the animals the T-tubes were left in for six months. Biliary calculi were found in two of the dogs that had T-tubes for 6 months.

BURNS PLEWES

The Treatment of Carcinoma of the Hypopharynx and Cervical Œsophagus.

O. F. GRIMES AND H. B. STEPHENS: *A.M.A. Arch. Surg.*, 72: 742, 1956.

Since carcinoma about the larynx is not effectually controlled by radiation therapy, especially if lymph node involvement is present, more frequent and more extensive surgical treatment is advocated. A series of 25 cases treated by the method first described by Wookey is here reviewed. There were four operative deaths and eight patients are still alive, the longest survival being 5½ years. Attempts were made to provide in a one-stage procedure a skin-graft tube for swallowing, but failures were the rule and staged operations for the grafting are satisfactory.

Though many of these patients were not cured and died of their disease, all were grateful for the palliation afforded by the operation even though the power of speech was sacrificed. BURNS PLEWES

Segmental Resection in the Treatment of Pulmonary Tuberculosis.

R. F. CORPE, J. L. SHEK AND J. A. COPE: *Dis. Chest*, 30: 183, 1956.

The authors review 182 consecutively treated patients, all having had segmental resections as well as other types of therapy for pulmonary tuberculosis. At the time of hospital admission 99.7% had moderate or far advanced pulmonary tuberculosis; 89% had positive sputum. All had similar therapy—bed rest, antimicrobial drugs, and excisional surgery—and 77% of them had received collapse therapy. Within a six-month period prior to surgery 57% had had positive sputum, and 92% had been positive during preoperative treatment.

The early mortality rate was 1.1%. The morbidity rate was 20%. All complications, except the two cases of cardiac arrest leading to death, were otherwise amenable to further treatment.

At present, 8 (4.3%) of the 182 patients are treatment failures. There were 3 deaths, 2 in hospital and 1 (suicide) in the post-hospital follow-up. There are 3

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in hospital with positive sputum whose treatment has not been concluded. There are 2 on the outside with positive sputum, 1 of whom had positive sputum 4 months ago and has no evidence of relapse clinically or by x-ray shadows. The other has positive sputum and relapse shown by x-ray film.

Of the remaining 176 (95.7% of the total), there are 49 who remain in the hospital with an average post-surgery stay to date of 8.5 months, and their therapy is successful to date. The other 127 discharged patients have an average follow-up since surgery of 22 months.

S. J. SHANE

OBSTETRICS AND GYNÆCOLOGY

Culdoscopy for Diagnosis in Infertility.

J. V. KELLY AND J. ROCK: *Am. J. Obst. & Gynec.*, 72: 523, 1956.

An analysis of 492 culdoscopies done for the diagnosis of sterility at the Free Hospital for Women in the ten-year period ending July 1955 showed that 417 (84.8%) were successful and 75 (15.2%) failed. When an attempted culdoscopy fails, the chances are about three out of four that an exploratory laparotomy will disclose pelvic lesions.

Procaine infiltration, now considered unsatisfactory, was the most common form of anæsthesia (56.1%). The second in frequency was spinal (32.1%). Other types included epidural procaine and intravenous Pentothal. In 33 cases no anæsthesia was given.

Culdoscopy revealed the cause of sterility by disclosing unexpected lesions in 34.1% of patients thought to be "normal".

Pelvic pathological conditions interfering with reproduction were found in 222 or 53.2% of the 417 successful culdoscopies.

The chance of pregnancy appears to be doubled if the culdoscopy-screened patient with lesions undergoes operation.

ROSS MITCHELL

Present Status of Plastic Operations on the Fallopian Tubes.

J. P. GREENHILL: *Am. J. Obst. & Gynec.*, 72: 516, 1956.

Data on 2,113 plastic tubal operations were assembled, following which operation there were 405 pregnancies, or 1 pregnancy after every 5 operations. There were only 313 living children, an incidence of 77.3% of the pregnancies, and a frequency of 1 living child after every 6½ operations. The presence or absence of ectopic pregnancies was specified in 286 pregnancies. In this group there were 45 tubal pregnancies; i.e., 1 ectopic pregnancy after approximately every 6 operations.

Results are still far short of what they should be to justify indiscriminate plastic tubal operations. The results of nonsurgical treatment of closed tubes are almost as good as those of surgery. Candidates for tubal plastic operations should be sent only to gynæcologists who are interested in the subject and are performing skilful operations.

ROSS MITCHELL

Pregnancy and Lupus Erythematosus.

E. A. FRIEDMAN AND J. W. RUTHERFORD: *Bull. Sloane Hosp. for Women*, 2: 40, 1956.

Case histories were reviewed of 188 female patients with lupus erythematosus at the Presbyterian Hospital, New York, for the 23-year period 1932-1955 and particularly of a group of 29 patients whose disease process was intimately linked with one or more pregnancies.

Lupus erythematosus does not specifically alter fertility but there is an increased incidence of premature births. The infants, if carried to viability, are apparently unaffected by the maternal disease. The large majority of patients with the acute and subacute disseminated form experience notable subjective relief in pregnancy and occasional reversals of laboratory findings as well. The disease process, however, is not apparently specifically affected by the pregnancy; exacerbations and remissions both occurred in nearly equal numbers, in early pregnancy. In the third trimester the disease becomes strikingly stable, and return to the pre-pregnancy condition occurs after confinement, usually within two months. Exacerbations are the rule.

Rapid acceleration of progression of the disease in association with pregnancy in patients with previously quiescent or mildly active disease has been seen. This occurs so infrequently, however, as to be considered a mere chance occurrence, the pregnancy being an unrelated, superimposed incident within the framework of the natural course of the disease.

ROSS MITCHELL

ORTHOPÆDICS

Meniscus Injuries of the Temporomandibular Joint.

C. M. SILVER, D. S. STANLEY AND A. A. SAVASTANO: *J. Bone & Joint Surg.*, 38-A: 541, 1956.

The authors consider that injuries to the meniscus of the temporomandibular joint are undoubtedly more common than is ordinarily supposed. They may not come to the attention of the orthopædic surgeon because the patient may consult either a dentist or an otolaryngologist for supposed tooth or ear trouble. The present authors have collected no less than 44 cases in which they have performed the operation of meniscectomy with excellent results. In half the cases no information could be given as to the cause of the condition, although inflammation, a history of wide opening of the mouth, direct trauma and malocclusion have been considered as etiological causes.

Symptoms are local and peripheral. Locally pain, snapping and crepitation are common, as is locking of the jaw. Peripherally there may be pain about the ear, tinnitus, pain referred to the top of the head or side of the jaw, burning of the tongue and a metallic taste in the mouth. On examination the joint is tender and mouth opening is limited, while snapping and crepitation may be heard by others as well as the patient. The jaw may be deviated towards the involved side. A radiograph should be taken to exclude other conditions and give information about the status of the joint.

In the present series, 40 of the 44 patients were women, mostly under 40 years old. In each case the patient was first referred to the dentist to see whether bite correction would be necessary. In early active stages of the condition, many patients may make an uneventful recovery if good apposition of the teeth is obtained conservatively. If pain persists or locking has occurred, excision of the damaged meniscus is indicated. A five-year follow-up of the patients after operation has not demonstrated any changes in the involved joint, in spite of the fact that it has been converted into one whose surfaces do not fit one another.

THERAPEUTICS

Clinical, Bacteriologic and Pharmacologic Observations Upon Cycloserine.

A. D. RENZETTI *et al.*: *Am. Rev. Tuberc.*, 74: 128, 1956.

Cycloserine has definite *in vitro* activity against tubercle bacilli in a range of concentration low enough to be attained in human blood. It has tuberculostatic rather than tuberculocidal activity. Observations *in vitro* indicate that it is a less active drug against tubercle bacilli than either isoniazid or streptomycin. Tubercle bacilli may emerge resistant to the drug after prolonged exposure.

Pharmacologically, cycloserine is absorbed easily and rapidly from the gastrointestinal tract, is distributed to lung, kidney, and brain in adequate concentrations (at least in the rabbit), and is excreted promptly in urine.

It has not been demonstrated that cycloserine is as effective as either isoniazid or streptomycin in tuber-

culous adults with far advanced pulmonary disease. It is active against streptomycin- and isoniazid-resistant tubercle bacilli and, therefore, may have limited application in patients with tuberculosis produced by such organisms.

On occasion cycloserine has a clear, unexplained central nervous system toxicity leading to the production of convulsions, which makes its use hazardous. The toxicity is not serious enough, however, to preclude its prescription with the proper indication. Other toxicity studies in man have demonstrated that, with 1 g. daily doses given for as long as 8 months, no adverse effects upon kidney, liver, or bone marrow develop.

Cycloserine is another antituberculous drug which may become a valuable tool in the therapy of the human disease. Virtually all evidence points to the conclusion that its activity is less than that of either streptomycin or isoniazid. More studies are warranted, before final definition of its usefulness can be estimated (including its use with either streptomycin or isoniazid), to determine its effect upon the emergence of drug-resistant variants.

S. J. SHANE

PATHOLOGY

Thymoma: A Review and Reclassification.

L. IVERSON: *Am. J. Path.*, 32: 695, 1956.

Thymoma taxonomy is here simplified. True thymomas usually do not metastasize. They are of two types: (1) those with myasthenia gravis, and (2) those without it. Large pale epithelial cells characterize the first type: these may be endocrine, accounting for the symptoms, and are often in clusters around blood vessels. Finely dispersed red granules were noted in the cytoplasm of the cells lining the vessels after staining with periodic acid-Schiff. These epithelial cells are mixed loosely with lymphocytes in a delicate stroma. In the second type the lymphoid and spindle cells and the stroma are all more prominent. Often mistaken for thymomas are the malignant seminomatous tumours of the mediastinum, and the benign localized hyperplastic mediastinal lymph node. The former has frequently a concomitant granulomatous reaction, and is radiosensitive. It is not a thymic carcinoma. The latter shows germinal centre alterations which may look like Hassall's corpuscles. Differential cytodiagnosis of these various tumours is given.

C. C. MACKLIN

The Pathology of Ischemia of Skeletal Muscle in Man.

R. E. SCULLY AND C. W. HUGHES: *Am. J. Path.*, 32: 805, 1956.

This is a study by former members of the Surgical Research Team in Korea based on various types of arterial injury sustained in combat. Specimens were obtained: (1) by biopsy at the time of injury, securing samples in which changes could be attributed to ischæmia rather than direct trauma; (2) surgical excision of degenerating muscle groups; (3) after amputation.

Previous literature dealing with work on arterial and venous interruption, both individually and together in the experimental animal, is reviewed and these findings are correlated with those observed in humans. As might be expected, these are very similar in many respects and depend on such factors as degree and period of obstruction as well as the duration of the recovery period before pathological examination is done.

Histological changes in the more complete ischæmia show a prominent accentuation of the cross striations, in addition to the longitudinal fibrils becoming more ill-defined and losing their wiry character. Roughly comparable findings are noted in the human lesion but here care must be taken to distinguish artefacts secondary to muscle contusion. These changes can be graded from complete necrosis of muscle with no evidence of inflammation or repair up to scarcely any demonstrable change. Between would be seen lesions with varying degrees of damage and reparative responses.

Grossly, these muscles some hours after injury are noted to be hard, tense and swollen. Later findings are those described as Volkmann's contracture due to muscle infarction, consisting of hard, homogenous yellow cores surrounded by scar tissue. These masses of necrotic muscle are enclosed successively by zones of histiocytes, fibroblasts and dense collagen.

The controversial contention that simultaneous ligation of veins reduced the incidence of gangrene in extremities where arterial ligation was carried out is referred to. It seems now that the studies of DeBakey and Simeone have more or less disproved the claim. Considering the gross congestive changes noted with pure ligation, followed by extensive fibrosis, it seems hard to accept the practice as beneficial.

A consideration of the arterial and venous spasm and sometimes irreversible changes which follow the use of the tourniquet reminds us that it must be used only when absolutely necessary. The appearance of a tense swelling, capillary engorgement, œdema, hæmorrhage and release of myoglobin all noted on release of the constriction as well as after the re-establishment of the arterial flow may accentuate the pathological changes.

Complete necrosis was encountered most often in the long slender muscles of the leg, while generally speaking the gastrocnemius was essentially normal. On the other hand, the soleus muscle seemed to suffer more. It is of interest to note that this is at variance with other experimental work.

The exact nature of pathogenesis of ischæmia is uncertain. A similarity was however noted between the changes of muscle ischæmia secondary to arterial trauma and those of the crush syndrome. Gross depigmentation of muscle similar to that in crush syndrome and even renal failure may be seen in cases of arterial injury without crushing. A number of excellent photomicrographs are presented to illustrate these findings.

ALLAN M. DAVIDSON

INDUSTRIAL MEDICINE

John Darwall, M.D. (1796-1833) and "Diseases of Artisans".

A. MEIKLEJOHN: *Brit. J. Indust. Med.*, 13: 142, 1956.

A thesis entitled "Diseases of Artisans with Particular Reference to the Inhabitants of Birmingham", written in Latin, was presented to the University of Edinburgh in 1821 by Dr. John Darwall, a physician of Birmingham. This document is of merit only from a historical point of view. In the present article, after a biographical note on John Darwall, the author gives his translation of the thesis together with the Latin original.

As related in the introductory part of the thesis, in the early days of the world, agriculture was the main form of labour. Crafts were few and it is probable that occupational diseases were equally few. With the development of various trades there came an increase in the number of such diseases. Either the materials used in the work or the method of working frequently caused illness among the tradesmen. Little research, however, had been carried out regarding these hardships and few attempts had been made to relieve them.

During the summer of 1820 Dr. Darwall, who had become interested in the work-people, inspected factories and homes in Birmingham. On these occasions he questioned the workmen personally on their health and in this way collected facts about the diseases of artisans. Additional information and advice was provided by the former president of the Medical Society. In Dr. Darwall's opinion the causes of ill-health arising from the numerous trades were fewer than the number of trades. He discusses these as follows: immoderate labour, muscular effort, posture, light and noise, variations of temperature, mechanical irritation, and chemical irritation. In some instances his own observations are supplemented by earlier ones of Ramazzini and several other investigators.

MARGARET H. WILTON

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OBITUARIES

DR. JERMYN OSCAR BAKER, 73, chief surgeon for the Northern Alberta Railways and the Edmonton division of the CNR, died in Ottawa, Ont., on October 24. Dr. Baker was born in Newington. After his graduation from Queen's University, Kingston, 1908, he was in charge of medical work for the Grand Trunk Pacific during its construction from Edson, Alta., to the West Coast. He did postgraduate work in New York, and served as medical officer with a British artillery brigade in World War I; Dr. Baker then settled in Edmonton where he founded the Baker Clinic, specializing in obstetrics and gynæcology. He taught these subjects at the University of Alberta. He was senior medical officer to the 20th Field Brigade.

Dr. Baker is survived by his widow and a daughter.

DR. GEORGE LYMAN DUFF, one of Canada's most distinguished pathologists and medical educators, died in Montreal on November 1 at the early age of 52. Dr. Duff, a native of Hamilton, Ont., was dean of medicine at McGill University. He graduated in arts in the University of Toronto in 1926 and in medicine in 1929, taking the David Dunlap Memorial Prize in psychology and psychiatry. In 1932 he was awarded the Ph.D. of the University of Toronto, together with the Starr Gold Medal, for a thesis on arteriosclerosis. In 1947, he became a Fellow of the Royal College of Physicians and Surgeons of Canada. This year the Royal Society of Canada awarded him the Flavelle Medal for outstanding scientific achievement.

In 1929 he joined the staff of the University of Toronto, but transferred to the pathology staff of Johns Hopkins University, Baltimore, in 1931, returning to Toronto in 1935 as a lecturer and later assistant professor of pathology. In 1939, he was appointed Strathcona professor of pathology and director of the Pathological Institute at McGill University in succession to Professor Horst Oertel. His research at McGill centred mainly round diseases of aging, pancreatic disease and atherosclerosis. He was in fact invited to a World Health Organization conference on atherosclerosis last year, as a mark of his international reputation, but was prevented by illness from attending.

In the educational field, it should be noted that Dr. Duff became Dean of the faculty of medicine in McGill University in 1949, and was an examiner in pathology first for the Medical Council of Canada and then for the Royal College of Physicians and Surgeons of Canada (1944-1955). He was appointed lecturer in medicine to the latter body in 1947.

Dr. Duff belonged to an impressive list of pathological societies, both national and international. He was a past president of the International Academy of Pathology, the Quebec Association of Pathologists, the American Society for the Study of Arteriosclerosis, the American Association of Pathologists and Bacteriologists, and the National Cancer Institute of Canada.

He served on the editorial board of several medical journals, including the *Canadian Medical Association Journal*, which he often helped with advice.

Dr. Duff is survived by his widow, the former Isobel Griffiths of Niagara Falls, Ont., two sons and two daughters.

Dr. Lyman Duff

An Appreciation

Lyman Duff came to McGill in 1939 and immediately established a high reputation as a teacher and administrator. He possessed a judicial frame of mind. Its chief characteristics were patience, complete impartiality and fairness, a wide outlook, and an entire absence of pet ideas and theories. He gave a fair hearing to all sides. Yet, having weighed a question he could come to a decision and present it cogently and convincingly. Nor was it easy to move him once he had made up his mind. He was neither overawed by those in authority nor neglectful of the opinions of lesser folk. Criticism and dissent neither irritated him nor awakened his slightest resentment and he was always ready to meet an objection with a reasonable compromise. His cool, steady and extremely competent mind was an excellent equipment for a Dean of a Medical Faculty and along with his conscientiousness and application explains his outstanding success in this office. His services to McGill Medical School will be long remembered.

C.P.M.

DR. LEWIS H. FRASER, a surgeon who worked in Peru for many years, died on October 18 in Saratoga Springs, N.Y. Dr. Fraser was born in Bermuda, and graduated from Queen's University, Kingston, Ont. He served with the army in World War I. Dr. Fraser was personal physician to the then Prince of Wales during a Royal Tour of South America. He retired a few years ago as head of International Petroleum's hospital at Talara, Peru.

Dr. Fraser is survived by his widow, two sons and two daughters.

DR. A. EDWARD LOGIE, aged 79, died in the Saint John General Hospital on October 24, after a short illness. Born at Tabusintac, Dr. Logie received his early education at Chatham and graduated in medicine from McGill in 1900. He practised first at Milbridge, Maine, and for the past 45 years had practised in Saint John. He served as a senior physician in the Saint John General Hospital and for the past several years had been on the consulting staff. He was Superintendent of the Evangeline Hospital for a long period and had had a long experience as an examiner for life insurance companies; for 45 years he was Chief Medical Examiner for the London Life Insurance Co. at Saint John. He served in the C.A.M.C. during the first world war. He was a Mason and a member of the United Church. He is survived by two sons, two daughters, eleven grandchildren and one great grand-daughter. Dr. Logie was really of the old school of physicians. He depended on inspection, auscultation, percussion and a careful and crafty history to establish his diagnosis. He was highly esteemed by his medical colleagues and the citizens of Saint John.

A.S.K.

DR. JENNIE HILL MITCHELL. We regret to announce the death—within a few days of each other—of Dr. Jennie Hill Mitchell, physician, and the Reverend Robert Alexander Mitchell, her husband, the parents of Dr. R. Morrison Mitchell of Sudbury, past president of the Ontario Medical Association and a member of the Executive Committee of the C.M.A. Dr. Robert Mitchell was a United Church Missionary in China for many years. He went to China for the Presbyterian Church of Canada in 1895 and served in that Church's mission in Honan province, China. Dr. Jennie Hill, then a graduate of the Ontario Medical College for Women, also went to China under the American Presbyterian Church at much the same time. They met and were married in 1900. They continued to work as a team in Northern China for over 40 years, before retiring to Toronto in 1937. Our sympathy goes out to Dr. R. Morrison Mitchell and the rest of the family in their sad bereavement.

DR. PETER WENGER, 48, director of the Fort William and District Health Unit, Ont., died on October 9, after a long illness. He was born in Fort William and graduated from Queen's University, Kingston, Ont., in 1935. Dr. Wenger practised at Timmins, Ont., from 1935-1940 and then returned to Fort William. During World War II he was doctor at the Canadian Car plant for two years. In 1950, Dr. Wenger obtained the Diploma in Public Health from the University of Toronto. He was medical officer of health in Kenora, Ont., in 1951 and became medical director for Fort William in 1952.

Dr. Wenger is survived by his widow and a daughter.

FORTHCOMING MEETINGS

CANADA

COLLEGE OF GENERAL PRACTICE OF CANADA, First Annual Scientific Convention, Montreal, Quebec. (Dr. J. Y. Tremblay, 3244 Beaubien, Montreal, Que.) March 4-6, 1957.

CANADIAN SOCIETY OF MICROBIOLOGISTS, Annual Meeting, London, Ontario. (Professor J. A. Carpenter, Department of Bacteriology, Ontario Agricultural College, Guelph, Ont.) June 10-12, 1957.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Banff Springs Hotel, Banff, Alta. (Dr. G. A. Henry, Secretary, 328 Medical Arts Bldg., Toronto, Ont.) June 17-19, 1957.

NINTH INTERNATIONAL CONGRESS OF RHEUMATIC DISEASES, Toronto, Ontario. (Ninth International Congress of Rheumatic Diseases, P.O. Box 237, Terminal "A", Toronto, Ont.) June 23-28, 1957.

UNITED STATES

INTERNATIONAL ANÆSTHESIA RESEARCH SOCIETY, Phoenix, Arizona. (Dr. A. William Friend, 13951 Terrace Road, Cleveland 12, Ohio.) April 1-4, 1957.

PAN AMERICAN ASSOCIATION OF OPHTHALMOLOGY, Fourth Interim Congress, in conjunction with National Society for the Prevention of Blindness, New York, N.Y. (Dr. Frank H. Constantine, 30 West 59th Street, New York 19, New York.) April 7-10, 1957.

PAN-AMERICAN CANCER CYTOLOGY CONGRESS, sponsored by the Southern Society of Cancer Cytology, the Cancer Institute, Miami, and the Cancer Cytology Foundation of America, Inc., Miami, Florida. (Dr. J. Ernest Ayre, New York University, Washington Square, New York, N.Y.) April 25-29, 1957.

SIXTH INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY, Washington, D.C. (Dr. Paul H. Holinger, 700 North Michigan Avenue, Chicago 11, Ill.) May 5-10, 1957.

SIXTH INTERNATIONAL CONGRESS OF BRONCHOESOPHAGOLOGY, Philadelphia, Pennsylvania. (Dr. Chevalier L. Jackson, Secretary, International Bronchoesophagological Society, 3401 N. Broad Street, Philadelphia 40, Pa.) May 12-13, 1957.

INTERNATIONAL AUDIOLOGY CONFERENCE, sponsored by National Science Foundation, St. Louis, Missouri. (Dr. Richard S. Silverman, Director, Central Institute for the Deaf, 818 South Kingshighway, St. Louis 10, Missouri.) May 14-16, 1957.

INTERNATIONAL VOICE CONFERENCE, Chicago, Illinois. (Dr. Hans von Leden, 30 N. Michigan Avenue, Chicago 2, Ill.) May 20-22, 1957.

OTHER COUNTRIES

FOURTEENTH INTERNATIONAL TUBERCULOSIS CONFERENCE, under the auspices of the International Union against Tuberculosis and the Tuberculosis Association of India, New Delhi, India. (Conference Secretariat, c/o Tuberculosis Association of India, 22 Red Cross Road, New Delhi, India; or International Union against Tuberculosis, 15 rue Pomereu, Paris 16e, France.) January 7-11, 1957.

NORTH AMERICAN CONFERENCE OF THE INTERNATIONAL FERTILITY ASSOCIATION, Monterrey, Mexico. (Dr. A. Salas-Guerra, Matamoros 362 Pte., Monterrey, N.L.) January 16-19, 1957.

INTERNATIONAL COLLEGE OF SURGEONS, 10th Biennial International Scientific Congress, Mexico, D.F., Mexico. (Dr. Max Thorek, International Secretary General, International College of Surgeons, 850 W. Irving Park Road, Chicago 13, Illinois.) February 24-28, 1957.

ANNUAL HEALTH CONGRESS, Folkestone, Kent, England. (Secretary, Royal Society for the Promotion of Health, 90 Buckingham Palace Road, London, S.W. 1, England.) April 30-May 3, 1957.

PROVINCIAL NEWS

SASKATCHEWAN

New regulations under the Hospital Standards Act of Saskatchewan have been recently announced in the *Saskatchewan Gazette* under date of September 21, 1956. In these regulations a Board of Conciliation has been established and as this is apparently a step forward in hospital-physician relationship, these regulations are quoted in part for your information.

"89. A physician who has been a member of the medical staff of a hospital and has been suspended or dismissed from the medical staff by the hospital board, or, who having been a member of the medical staff has not been reappointed at the end of the year to the medical staff, or, who has applied but has been refused membership on the medical staff of a hospital, or, who has been restricted or limited as to professional privileges in the hospital, may protest such action by sending a letter of protest to the board.

"90. If the hospital board does not reinstate, or appoint the physician as a member of the medical staff, or otherwise deal with the matter under protest within ten days of receipt of the letter of protest, either the hospital board or the physician may refer the matter complained of to the Minister for consideration by a board of conciliation.

"91. The Minister may appoint a board of conciliation, comprised of one person nominated by the Saskatchewan Hospital Association or the Catholic Hospital Conference of Saskatchewan, one person nominated by the College of Physicians and Surgeons of Saskatchewan, one person representing the Department of Public Health, and such other members who may in his opinion be best qualified to examine the matters under dispute. The Minister may appoint the chairman of the board of conciliation.

"92. The board of conciliation shall examine the matters complained of and may hold hearings to receive the submissions of interested parties. The board of conciliation may hold hearings in public or *in camera* and may receive and accept such evidence on oath, affidavit, or otherwise, as in its discretion it may deem fit and proper, whether admissible as evidence in a court of law or not, and the board and each member thereof shall have all the powers conferred upon commissioners by sections 3 and 4 of the Public Inquiries Act.

"93. Upon completion of its hearing the board shall send a summary of its findings of facts, its conclusions and recommendations to the parties to the dispute and to the Minister, and shall make available for publication such of its conclusions and recommendations as it may in its discretion deem advisable.

"94. The expenses incurred by each member of the board of conciliation in serving as a member of such board shall be paid by the association or organization which nominates him, providing that the Minister may pay the expenses of other persons who are named by the Minister as members of the board. Such remuneration shall be in the amount of fifteen dollars ($15.00) *per diem* for each day a member is present when the board sits, plus actual expenses incurred in travel from his place of residence to meetings of the board and return therefrom, and for room and meals while attending meetings of the board.

"95. Every hospital may be visited at any time by the Minister, or any of his inspectors, or any person delegated by the Minister, for the purpose of an inspection or inquiry regarding the physical plan, equipment and furnishings, operation, or the administration in general of the hospital.

"96. The Minister when he deems it expedient to cause inquiry to be made into and concerning any matter connected with the administration or conduct of the affairs of a hospital, or which is in his opinion of sufficient public importance, may appoint a board to make such inquiry and to report thereon.

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"97. A board of inquiry and each member thereof, appointed under authority of section 96, shall be governed as to rights and privileges of sections 92, 93, and 94, above."

A three-storey extension to the Administrative Wing of the Swift Current Union Hospital and a 76-bed nurses' residence has been approved by the Saskatchewan Hospital Planning Commission Board, the Chairman, Mr. I. Hanson, announced recently.

The extension will provide an additional 41 beds for the Union Hospital, which at the present time has a capacity of 114. The combined costs of the hospital extension and nurses' residence would amount to approximately $500,000. Of the three storeys to be built, the centre storey will not be finished. This will be ready when further extensions are required. This vacant floor would allow for a further increase of 21 beds when the need arises.

The nurses' residence will consist of a full basement and two storeys, and will provide living accommodation for 76 nurses.

The Chairman, Mr. Hanson, stressed that the old residence, which was formerly the hospital here, would not be sold but would be retained by the Hospital Board for health services in the future, probably for outpatient and pathological services.

Awarding of two hospital construction grants totalling $6,856 to the Balcarres Union Hospital Board has been announced by the Saskatchewan Department of Public Health. These grants were being made to assist the Board toward construction of two health centres, with a $3,186 grant for a projected $12,265 health centre at Lemberg and a $3,670 grant for a projected $20,000 centre at Lipton.

A substantial increase has been noted in the number of motor vehicle accidents, road deaths, injuries and property damage, reported in Saskatchewan in the first seven months of this year, compared with figures for the corresponding period of 1955.

A meeting of the Saskatchewan Psychiatric Association was held at the Valley Centre, Fort Qu'Appelle, on October 23. Among the items discussed was a brief which it is planned to present to the Minister of Public Health.

The 49th Annual Meeting of the College of Physicians and Surgeons of Saskatchewan and the Canadian Medical Association, Saskatchewan Division, was held in Saskatoon during the second week of October. It was one of the most successful conventions in the College's history with a total registration of over 400 physicians. The clinical program was well received, with the Munroe Lecture, sponsored by the Saskatchewan Division of the Canadian Cancer Society, given by Dr. James Baldwin of the Pack group in New York City. Dr. J. C. Luke and Dr. J. Genest, together with Dr. R. Lemieux, were members of the C.M.A. team and made most appreciated contributions to the program.

The Honourable T. J. Bentley, formerly Minister of Public Health, Province of Saskatchewan, and now Minister of Social Welfare, called for real leadership in all aspects of health by the medical profession. He particularly stressed the value of periodic examinations, adding that people in the health field must give leadership to the public in finding ways to implement this and other recommendations.

The social aspects of the program were well attended and much enjoyed. Three District Societies, namely Regina, Moose Jaw and Saskatoon, competed for the Ritchie Cup by presenting skits of a high quality. The Ritchie Cup was won by the Moose Jaw and District Medical Society.

Next year's convention, which will be the 50th, will be held in Moose Jaw as the guests of the Moose Jaw and District Medical Society. Planning is already under way for this important event.

Sir Geoffrey Keynes, a distinguished scholar in both medical and humanitarian fields, visited the University of Saskatchewan as the Sir Arthur Sims Commonwealth Travelling Professor of the Royal College of Surgeons, England, during early October.

Sir Geoffrey addressed the medical students, speaking on "William Harvey", and an open joint meeting of the Humanities Association and the Faculty Club on "William Blake's Illuminated Books". He also spoke to members of the medical profession in Saskatoon on "The Surgery of the Thymus Gland". G. W. PEACOCK

ONTARIO

With completion in 1957 of the Ontario Government's poliomyelitis vaccination program it is proposed that polio vaccine be added to the present list of vaccines, toxoids and other biological products distributed without charge to the public through the medical profession. The 1957 program has been launched with shipments of vaccine to many local health departments. This distribution will continue throughout the winter and spring in accordance with the needs of each community.

It is the objective of the program for the coming year to complete the administration of at least two doses of poliomyelitis vaccine to all pre-school, elementary school and secondary school children in the province in advance of the 1957 polio season.

"The majority of elementary school children have received two doses of vaccine and a limited number have received their third dose as well," the Hon. Mackinnon Phillips, Minister of Health, stated. "This means that we face the task of giving vaccine to the following groups of children before the end of June 1957: two doses of vaccine to pre-school children; two doses to elementary school children who have not yet received vaccine, or have received only one dose; two doses to secondary school children, including children in continuation and vocational schools; the third dose of vaccine to those children who received two doses in 1955; the third dose of vaccine to those children who received two doses in 1956."

NEW BRUNSWICK

Dr. J. A. Caskey, Radiotherapist at the Saint John General Hospital, discussed research in cancer at a training seminar conducted at Sackville, N.B., by the Maritime branches of the Canadian Cancer Society.

The Department of Health in New Brunswick is continuing a survey of water supplies in rural areas of the province, and at present the Nashwaaksis area is the centre of activity. Dr. D. F. V. Brunsdon, Director of the Fredericton Regional Laboratory, is supervising these tests.

All four hundred and forty new entrants to Teachers' College at Fredericton were examined by teams of nurses, x-ray staff and technicians in the provincial capital, followed by clinical examinations by public health doctors directed by Dr. J. A. Melanson, Chief Provincial Medical Officer, and Dr. R. S. Langstroth, Director of Dental Health.

Sponsored by the postgraduate department of Dalhousie University and the N.B. Medical Society, an extramural meeting on September 25 brought Dr. J. A. Lewis, University of Western Ontario, and Dr. J. Arnold Noble of Dalhousie University to Fredericton.

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Dr. Noble spoke on "Surgery of the peripheral vascular system" and Dr. Lewis discussed "Hypertension, diagnosis and treatment". Dr. Hector McKinnon of Fredericton presented cases, which were discussed by the visiting specialists. The previous day the same speakers spoke to a medical gathering at Bathurst.

The Medical Societies of Kings, York, Sunbury and Saint John were privileged to hear an address by Dr. Harold E. Taylor, Professor of Pathology of the University of British Columbia, on "The prognosis of pigmental skin tumours" at Saint John on September 23. Dr. Taylor stopped over in New Brunswick on his return journey after appearing as a guest speaker at the Dalhousie Refresher Course at Halifax.

At the annual meeting of the New Brunswick Tuberculosis Association it was reported by Dr. G. E. Maddison, Medical Director of the Association, that the death rate per 100,000 of population had dropped to 7.7 in 1955 compared to 9.1 in 1954.

Dr. J. A. Melanson, Chief Medical Officer of the New Brunswick Department of Health, has been honoured by the Royal Society of Health by being selected for membership in this, the largest society of public health workers.

Dr. John Nash, Chief Psychologist at the Provincial Hospital, Lancaster, N.B., has resigned to accept duties in the University Hospital, Saskatoon, Sask.

The provincial laboratories of New Brunswick continue to prepare technicians for certification as specialists by the Canadian Society of Technologists. Four such specialist awards have been granted in the past twelve months. Dr. R. A. H. Mackeen is director of the laboratories.

The Hon. J. F. McInerney, M.D., Minister of Health for N.B., with his Chief Medical Officer, Dr. J. A. Melanson, met the superintendents of the N.B. Sanatoria at the Jordan Memorial Sanatorium on September 25. Discussions included facilities for drug therapy for sanatoria patients, home conditions of patients under treatment with adequate visiting by trained workers, and the fall program of pulmonary surgery. The following physicians were in attendance: Dr. G. E. Maddison; Dr. E. Duguay, Bathurst; Dr. R. LeBlanc, Riverglade; Dr. R. J. Collins, Saint John; Dr. P. M. Knox, Moncton.

Dr. R. A. H. Mackeen, Director of Provincial Laboratories, Department of Health of New Brunswick, was elected Vice-president of the Forensic Society of Canada at the annual meeting held in the Seigniory Club, Quebec.

A one-day clinic sponsored by the New Brunswick Provincial Department of Health was conducted by Dr. A. F. Torrie, Orthopædic Specialist of Fredericton, at Edmundston; children and adults were interviewed and examined. Many of these were polio cases but crippled children with other abnormalities were included.

The N.B. Division of the Canadian Red Cross Society honoured a group of New Brunswick doctors for their services to the Junior Red Cross program for crippled children. The following physicians received the "Red Cross Badge of Service": Dr. D. R. Macrae, Dr. A. D. Gibbon, Dr. G. W. A. Keddy, Dr. T. E. Grant, Dr. E. W. Lunney, Dr. J. L. Sullivan, Dr. R. T. Hayes and Dr. George Skinner.

A. S. KIRKLAND

BOOK REVIEWS

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE. E. H. Rubin, Professor of Clinical Medicine, Albert Einstein College of Medicine, Yeshiva University, New York, N.Y. 288 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $13.75.

The author, who already has one widely read textbook on diseases of the chest to his credit, presents another work in a novel manner. The new volume discusses those diseases which may involve many organs or tissues of which the lung is one. While the pulmonary features and appearances of the conditions are stressed, all aspects of disease are dealt with, including illustrative case histories, profusely illustrated with excellent photographs, roentgenograms and photomicrographs. A physician of wide experience, he places much emphasis on the roentgenographic features of these diseases, many of which are obscure in their etiology and confusing in their differentiation. Included in the text are such conditions as the histiocytoses, hæmosiderosis, the "collagen" diseases, neurocutaneous diseases, sarcoidosis, Hammon-Rich syndrome, pulmonary hypertension, azotæmia with pulmonary manifestations, pulmonary embolism and infarction. (The reviewer could find only one sentence referring to agammaglobulinæmia and its pulmonary manifestations and no reference to the Stevens-Johnston mucosal-respiratory syndrome.)

While stressing the value of the clinical history and a thorough physical examination, the author states that "in the diagnosis of obscure systemic disease with pulmonary lesions, physical signs are usually lacking and one may have to resort to all available diagnostic measures." With this in mind an informative chapter on laboratory and exploratory aids is presented, including sputum examination for bacteria, fungi and exfoliated cells; blood examination including the L.E. test; skin tests and exploratory examinations such as lung biopsy and scalene node biopsy.

This book is excellently prepared and presented and is highly recommended to internists, radiologists and indeed to anyone dealing with problems in diagnosis of diseases in which pulmonary changes are encountered.

PSYCHOPATHOLOGY OF CHILDREN WITH ORGANIC BRAIN DISORDERS. Edited by Lauretta Bender, Professor of Clinical Psychiatry, New York University College of Medicine, N.Y. 151 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $6.00.

This, the fourth volume of the Bellevue Studies of Child Psychiatry, consists of a collection of papers written by Paul Schilder, Lauretta Bender, A. A. Fabian, A. A. Silver and H. Caplan. Like the other books in this series, Paul Schilder's influence is dominant throughout. He is the author of about one-half of the book, and the other half directly reflects his points of view.

The subject material includes the psychological implications of motor development, the psychology of children with organic disturbances of the cerebellum, psychiatric problems in the organic brain disorders of children, personality problems of the child with a head injury, body image problems of the brain-damaged child, and psychological problems and their management in the brain-damaged child. Of these various chapters perhaps the most valuable to the child psychiatrist is the final chapter, which is in many ways a summary.

The authors include the following with the biological or organically determined behaviour disorders: childhood schizophrenia, mental deficiency, cerebral palsy, encephalitis, and encephalopathies of various types, the language and learning retardations of maturational origin (reading disabilities, etc.). These behaviour disturbances are considered to arise from factors within the individual and not from external factors and environmental stresses.

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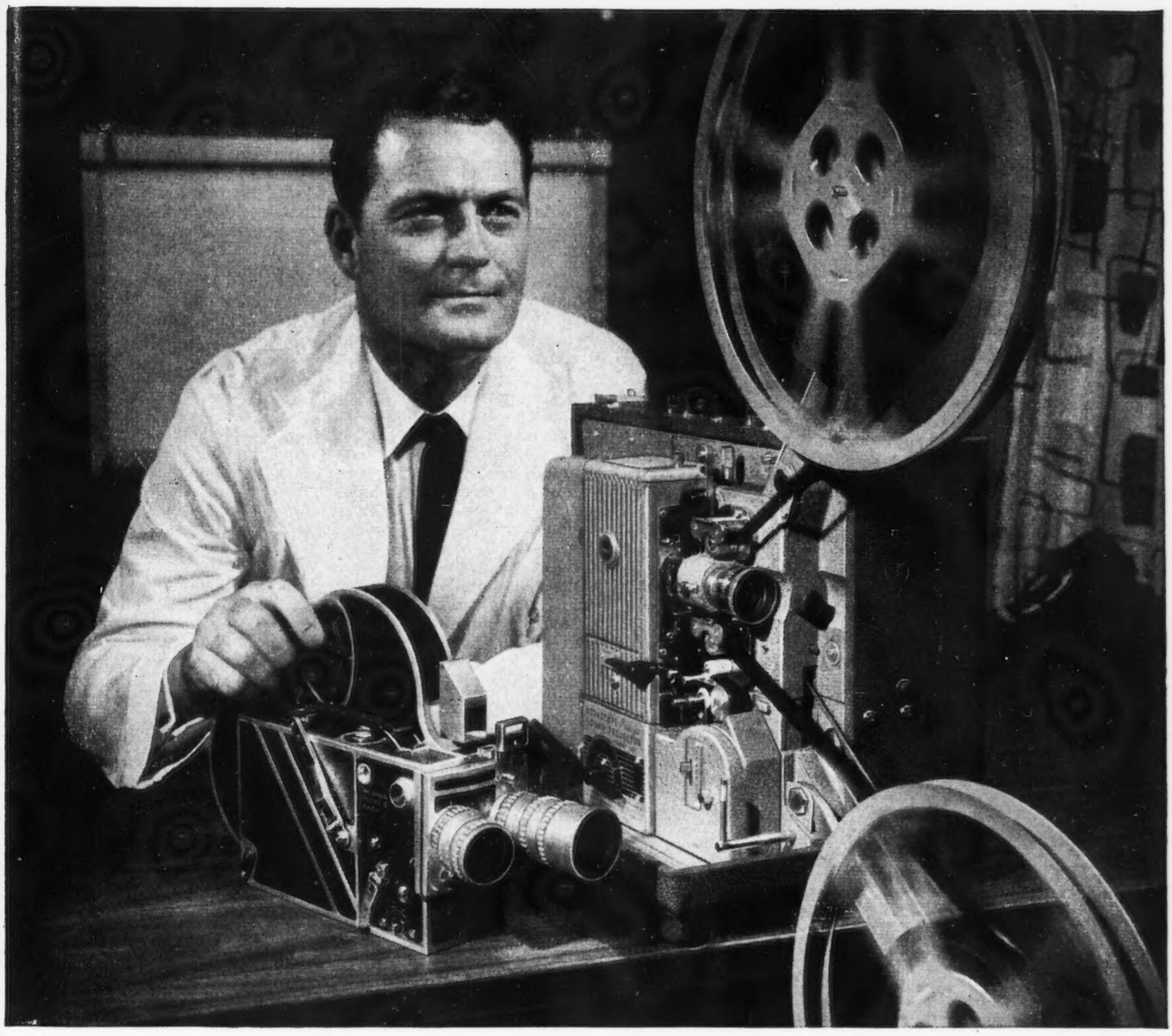

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The common patterns of behaviour associated with these syndromes include: (a) disorganized, regressed or retarded maturation in motor perception and integrative areas; (b) severe anxieties; (c) problems of self concept, body image, and identification; (d) increased need for human support and affection.

The authors stress that the examination of the brain-damaged child requires different techniques from those used with adults. This is particularly true of the neurological examination and one must think in terms of observed neurophysiological patterns as exemplified by postural reflexes. The neurological examination of these children needs to evaluate patterns of reflex behaviour such as sucking and grasping, the Moro reflex, the tonic neck reflex and the locomotor reflex patterns.

The core of therapy seems to be warm support and affection by those adults dealing with the brain-injured child. It also includes the gratification of the basic needs of these children with an extension, if necessary, of the period of normal dependency. It also includes an understanding of the limits and capacities of these children in order that the demands upon the child will be within his capacity. At the same time it is necessary to understand the compensatory behaviour of these children and to have a broad tolerance for these patterns of behaviour. Unfortunately, however, the portion of the book devoted to therapy consists of only a few pages towards the end of the final chapter.

Children treated in this way from the time of birth or from the time of the injury will have a much better prognosis than we have been accustomed to expect. In many instances the intellectual functioning will be adequate, as the intellectual retardation is more often apparent than real and depends upon isolation, blockage due to anxiety and the normal patterning of impulses. However, there will always be a number of these children in whom the organic damage has so affected the cerebral cortex that they are capable of functioning only as retarded individuals.

TUMORS OF THE SKIN. H. Conway, Professor of Clinical Surgery, Cornell University Medical College, New York. 267 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $14.75.

This book deals with benign and malignant tumours of the skin and subcutaneous tissues. The word tumour is used in its widest sense: the book covers many divers conditions such as rhinophyma, cysts, sinuses, fistulæ, foreign body reactions, and acanthosis nigricans, as well as most of the usual tumours. There are 178 excellent photographs, photomicrographs and schematic drawings illustrating surgical techniques. As the book is only 257 pages in length, each type of tumour is dealt with as briefly as possible, although there is considerable detail on melanomas, nævi, carcinomas of the skin and hæmangiomas. The author is to be commended for this emphasis on the histopathological features. This book is written by a surgeon for surgeons and, logically, the emphasis throughout is on surgical treatment. There are numerous references throughout, and an author and detailed subject index at the back.

With few exceptions, the material is well presented and accurate. A clear distinction between epidermal and cellular nævi is not found. Under the term "papilloma" the author discusses seborrhœic keratosis, cutaneous tags, and various types of epidermal nævi, although these are not designated as such. This tends to be somewhat confusing. Warts are said to turn to cancer if irritated. As this does not apply to infectious warts (verrucæ), it is hard to understand just what the author means by the term "warts". Notwithstanding the advertising material on the jacket which states that "all known varieties" of skin tumours are considered, this is not so. This book is not, nor is it intended to be, an exhaustive treatise on tumours of the skin. Many unusual and rare forms have been omitted. Perhaps some mention should have been made of dermatofibroma and keratoacanthoma.

All in all, however, this is a very good book with excellent photographs and adequate coverage of the common and not so common tumours of the skin.

SUBPHRENIC ABSCESS. H. R. S. Harley, Consultant Thoracic Surgeon, United Cardiff Hospitals and Welsh Regional Hospital Board. 216 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. $8.50.

This monograph summarizes in an orderly manner the pathogenesis of subphrenic abscess, using an analysis of 188 cases and a review of the surgical literature as a basis for authoritative opinions concerning the clinical course and a rational form of treatment for this condition. Modern concepts regarding the pertinent anatomy of the upper abdomen and the manner in which the various compartments are infected have been carefully and analytically reviewed with particular emphasis upon the etiology of associated thoracic complications. Suggested therapy follows classical lines, stressing the importance of the extraserous approach and the value of antibiotic therapy.

Nevertheless a major criticism develops from the failure of the author to take cognizance of the frequency with which the routine use of antibiotics may camouflage the diagnosis, rendering the problem one posing increasingly difficult therapeutic issues. No note is made of the significance of postoperative pneumoperitoneum, the possibility of increasing frequency of staphylococcal infection, and the potential value of antibiotics or chemotherapeutic agents other than penicillin.

With these criticisms in mind the basic information presented is fundamentally sound and, as such, represents a worthwhile contribution to our knowledge of this important lesion.

TECHNIQUES IN BLOOD GROUPING. I. Dunsford, Senior Scientific Officer, and C. C. Bowley, Director, Regional Blood Transfusion Centre, Sheffield, England. 250 pp. Illust. Oliver and Boyd, Edinburgh; Clarke, Irwin and Company, Limited, Toronto, 1955. $5.00.

This small book is a laboratory manual of the various techniques used in blood grouping tests. The first part of the book discusses the theoretical aspects of blood grouping, the principles involved in the detection of antigens and antibodies, the use of controls in testing and the causes of error in testing; and there are more notes on the organization of blood tests. The second section is devoted to detailed, step-by-step descriptions of the various tests used in blood grouping. Section III comprises a complete glossary of terms. The loose-leaf binding of the book makes it convenient to use on the laboratory bench.

This manual can be especially recommended to all those who have to do with the practical aspects of blood grouping. The brevity of the theoretical discussion sometimes leads to an unfortunate oversimplification of ideas, e.g. in the discussion on the role of electrical forces in agglutination. A few rather loosely worded sentences might be criticized, but they in no way detract from the understanding of this very useful book.

THE CORNEA. Charles I. Thomas, Associate Clinical Professor of Ophthalmology, Western Reserve University School of Medicine, Cleveland, Ohio. 1318 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. $33.00.

The important feature of this book is that it is comprehensive. Anatomy, embryology, physiology and pathology, congenital anomalies, dystrophies, inflammations, manifestations of systemic, metabolic, contagious and skin diseases, tumours, injuries, various forms of treatment and surgery are all included. More profound and thorough discussions of many of the subjects may be

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found elsewhere in the literature, but nowhere is so much material on the cornea gathered within one cover. It is to the author's credit that he has maintained a high standard throughout a broad subject.

The discussion of the normal and pathological physiology of the cornea is particularly worthy of note. In recent years there have been many clinical observations of physiological significance. These have been faithfully recorded, and, with the discussion of experimental physiology of the cornea, make a valuable section of the book.

The various corneal dystrophies are well described. An excellent addition to the book is a group of 21 coloured plates which beautifully portray various abnormalities of the cornea.

The description of surgery of the cornea is well organized, comprehensive, in fact well worth reading. The indications, techniques and results of various types of keratoplasty are discussed with intelligence and with care.

TEXTBOOK OF UROLOGY. V. F. Marshall, Associate Professor of Clinical Surgery (Urology), Cornell University Medical College, New York. 268 pp. Illust. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1956. $5.50.

This textbook of urology, by a most eminent and highly respected member of the urological fraternity, succeeds admirably in its aims.

The contents of the book are directed at the student and the general practitioner, and to both groups provide an informative and concise presentation of almost all aspects of urology, from the most common disorders to brief but clear mention of the rare but interesting urological upsets.

Dr. Marshall emphasizes very well the need for systematic study of the patient, in relation to disorders of the urinary and genital tracts. There is a liberal use of diagrams and charts which add much to appreciation of the text.

To mention a few of the useful sections of the book, there is detail on such subjects as the interrelationship between obstruction and infection, stone formation, neurogenic upsets, cause and treatments of various types of urethritis in both male and female, a discussion of impotence, a method of investigation of fertility in the male and the proper management of undescended testicle.

This volume is heartily recommended; it is interesting to read, easy to understand, and handy to refer to when needed. It is a short volume of around 250 pages, with excellent print, and has all the information needed on this particular specialty for the student and non-specialist in practice.

A MODERN PILGRIM'S PROGRESS FOR DIABETICS. G. G. Duncan, Clinical Professor of Medicine, Jefferson Medical College, Philadelphia, Pa. 222 pp. Illust. W. B. Saunders Company, Philadelphia, 1956. $2.50.

The story in this book carries it along easily. Margaret MacDowell, B.A., the heroine, works in the social service department of a large hospital. A newly diagnosed diabetic, she meets all types with this disease. There is the overweight Italian woman, the overactive club woman who has no time for her own care and comes to the inevitable tragic end, the child in coma and the adolescent in reaction and the business man who half controlled his diabetes only to die of heart disease. Margaret is both intelligent and attractive. She marries the intern and they have two healthy children.

The book is filled with everyday advice plainly stated. Thirteen diet lists given both as exchanges and in grams are set out in detail. The book will be useful for persons of all ages with diabetes and also for their physicians.

MEDICAL NEWS *in brief*

(Continued from page 940)

NEUROTROPIC DRUGS AND CHOLESTEROL LEVEL

According to Myasnikov (*Klinitsheskaya Meditsina,* 34: 65-69, 1956) disturbances of cholesterol level and their relation to the cause of atherosclerosis suggest a thorough study of the neuro-regulatory mechanisms involved. A close relationship exists between the condition of the central nervous system and the metabolism of lipoid substances. Organic diseases of the nervous system as well as neurotic conditions and emotions have their influence upon the cholesterol titre in the blood. This titre can be influenced by the administration of neurotropic drugs, as is demonstrated in the following experiment. Ninety-six patients, among them 79 with atherosclerosis, were divided into four groups and were given a single dose of the sedatives Sodium Amytal and chloral hydrate and of the stimulants phenamine and caffeine, respectively. Immediately before and one to two hours after the administration of the drugs the blood level of free as well as of esterified cholesterol was measured. Following the administration of the stimulants a rise in cholesterol level was registered in all cases; the sedatives had an opposite effect. Both free cholesterol and its esters were affected. In 14 cases the levels of lecithin were also measured. Lecithin plays a part in stabilizing cholesterol in the colloidal state. Both after a sedative and after a stimulant the lecithin level showed a rise. It did not follow the contrasting pattern of behaviour of cholesterol.

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THE WILLIAM OSLER MEDAL OF THE AMERICAN ASSOCIATION OF THE HISTORY OF MEDICINE

In order to stimulate interest and research in medical history among students of the medical schools of the United States and Canada, the American Association of the History of Medicine has established a medal that will be granted annually to the author of the best student essay submitted to the Association. The medal has been named in honour of William Osler, who more than any other academic teacher succeeded in creating among students enthusiasm for the history of medicine.

The Association will consider unpublished essays by men and women who were students in schools of medicine and had not yet obtained their doctor's degree at the time the essay was written. To be considered, an essay must be submitted before or within one year after the author's graduation. Essays that are the result of original research will be given preference, but the Association will also consider essays which, without being the result of original research, show an unusual appreciation and understanding of historical problems.

Essays should not exceed 10,000 words in length.

Essays must be sent before March 1, 1957, to: Dorothy M. Schullian, Ph.D., Chairman, National Library of Medicine, History of Medicine Division, 11,000 Euclid Avenue, Cleveland 6, Ohio.

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GASTRO-ŒSOPHAGEAL REFLUX IN INFANCY AND CHILDHOOD

Plarre, a Melbourne radiologist (*M. J. Australia,* 2, 241, 1956), discusses gastro-œsophageal reflux in infancy and childhood on the basis of 35 cases examined at the Royal Children's Hospital, Melbourne, with symptoms during their first year of life. These cases have been followed up for periods of from one to five years, and all but one have run a benign clinical course. The exception had persistent symptoms and has developed a large chronic peptic ulcer in the small hiatus hernia. The hernia has recently been excised. The author finds it difficult to determine the factors responsible for deviation from the usual benign course, and progression to fibrous stricture or chronic ulcer formation. It is clear that a hiatal defect may be present early in life without necessarily causing reflux. It is also clear that in cases of reflux with minor hiatal defect, the symptoms may subside, though reflux may persist long after the symptoms have subsided under medical control, and even after surgical treatment. Diagnosis of impending fibrous stricture is difficult in a young child. There is no

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MEDICAL NEWS *in brief*

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parallel between the degree of dysphagia and the severity of the stricture. Careful correlation of clinical, radiological and endoscopic findings is necessary for accurate diagnosis. Though endoscopy is hardly warranted as a routine investigation in young babies who are vomiting, a planned study of a small number of cases, if controlled by biopsy, might yield further data of value.

PAROTID SURGERY AND THE FACIAL NERVE

Beahrs and L'Esperance from the Mayo Clinic (*J.A.M.A.*, 162: 261, 1956) point out that efforts to remove parotid tumours have frequently been ineffectively conservative because of fear of inflicting damage on the facial nerve. They deprecate attempts at local excision or enucleation of tumours, which they think is responsible for the high rates of recurrence. They advise that in every case the stem of the facial nerve should be identified after it leaves the stylomastoid foramen and the branches then traced peripherally under direct vision. The superficial portion of the gland is separated from the branches of the facial nerve by blunt dissection, and as long as dissection remains superficial to the nerve, there is no danger of damaging the latter. For a benign tumour of the superficial portion of the gland, superficial parotidectomy is indicated. If the tumour is situated deeper, a total parotidectomy is indicated. If malignancy of the tumour necessitates removal of the facial nerve, a nerve graft should be used at the time of operation if possible, to bridge the gap as the initial step in treatment of the resulting cosmetic deformity. If not, other plastic procedures can be tried.

FUNGUS DISEASES OF LUNGS AFTER TREATMENT WITH ANTIBIOTICS

In a paper by Gasilin and Filipovich (*Klinitsheskaya Meditsina*, 34: 61, 1956) reference is made to several Russian authors who report appearance of candidomycosis (moniliasis) following prolonged treatment with antibiotics both in human patients and in experimental animals. Parasitic growth of the fungus is attributed to the absence of bacterial flora and to a disturbance in the vitamin level as well as to the general weakening of the organism. The authors report their observations on six patients whose sputum revealed the yeast-like fungus *Candida*. Four of the patients showed the characteristic symptoms of candidomycosis. Fluoroscopy of the lungs confirmed the diagnosis. All patients had been treated with penicillin for various severe conditions. Discontinuation of the antibiotic treatment brought about marked improvement. In some cases favourable results were obtained by substituting sulfanilamide preparations for antibiotics. The authors point out that, although it is not known whether this fungus disease is contagious, precaution should be taken to isolate the sick. The reported results corroborate the findings of other authors.

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MEDICAL NEWS *in brief*

Continued from page 55)

THE RESULTS OF L-TRIIODOTHYRONINE IN PATIENTS WITH METABOLIC INSUFFICIENCY

Tittle (*J.A.M.A.*, 162: 271, 1956) gives a preliminary report of the results of treatment of patients with metabolic insufficiency by means of 3,5,3′-L-triiodothyronine. The eight patients concerned (five females and three males between the ages of 22 and 55 years) had basal metabolic rates between –28 and –36% and complained of feeling tired easily, and of stiffness of muscles and joints, sensitiveness to cold, constipation, and other hypothyroid symptoms. Only very slight relief of symptoms had been obtained with desiccated thyroid. Apart from the BMR, other thyroid function values were within normal limits.

L-triiodothyronine was given in increasing doses to a maximum of 50-100 micrograms daily. Within one to two months the chronic fatigue and muscle and joint aching had disappeared in six of the eight patients. Basal metabolic rates rose to –16% or higher. Two patients developed insomnia, nervousness and palpitations, but withdrawal of the drug caused disappearance of these effects within several days.

It is concluded that L-triiodothyronine is a rapid and effective metabolic stimulant and therapeutic agent for treating metabolic insufficiency.

FEBRILE CONVULSIONS IN INFANCY AND CHILDHOOD

Opinions on the outlook for children who have febrile convulsions early in life are still sharply divided. Cary of the Institute of Child Health, Sydney, Australia (*M. J. Australia*, 2: 254, 1956), studied 100 cases of infants and children admitted to a Sydney hospital with convulsions, during the period 1943 to 1945. He omits from his series all forms of convulsions with a known underlying cause (for example, severe birth trauma, encephalitis, or intoxications). The commonest age at the initial attack was from six to 24 months. Eighty-five per cent of the children had no more convulsions after the age of six years. Ten years after the initial convulsion, only six children were still suffering from convulsions and were regarded as epileptics. This study therefore suggests that the prognosis of febrile convulsions must be considered, though it is difficult to predict which cases will go on to epilepsy. Cary does not therefore consider it justifiable to give routine anti-epileptic treatment to such patients.

BLOOD CULTURE IN BACTERIAL ENDOCARDITIS

When a patient is suspected of having subacute endocarditis, the question arises how many blood cultures should be taken to confirm the diagnosis before therapy is begun. To throw light on this problem, Belli and Waisbren from Milwaukee (*Am. J. M. Sc.*, 232: 284, 1956) studied 82 bacteriologically proven cases of subacute

bacterial endocarditis to determine how many blood cultures had been necessary before a positive result was obtained. They found that 52 of the cases had been diagnosed on the results of the first blood specimen, while 77 out of the 82 had given a positive blood culture within the first five cultures. In no case were more than ten cultures necessary to make the diagnosis. It would seem therefore that if five blood cultures have been sterile, it is justifiable to begin therapy in order to reduce valve damage and other complications.

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BAHAMAS CONFERENCE

The Bahamas Branch of the British Medical Association announces that it is holding a Bahamas Medical Conference in Nassau on December 1-15, 1956. The meeting is at the Emerald Beach Hotel, Nassau. There is a program of lectures and other teaching activities which includes contributions from various eminent authorities in the United States, such as Dr. Claude Beck of Western Reserve University, Cleveland, Dr. Edward D. Freis, Chief of the Medical Service, Veterans Administration Hospital, Washington, D.C., Dr. C. F. Geschickter, Professor of Pathology, Georgetown Medical Center, Washington, D.C., and Dr. Thomas W. Mattingly, Chief of the Cardiology Service, Walter Reed Army Hospital, Washington, D.C. Cases will be shown and ward rounds will be conducted at the Princess Margaret Hospital and other medical institutions on the island, and lectures and discussion groups will be held at the hotel.

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MEDICAL AND BIOLOGICAL APPLICATION OF RADIOACTIVE ISOTOPES

An extension course on the medical and biological application of radioactive isotopes is being given at McGill University by Dr. J. Sternberg, of the Institute of Microbiology and Hygiene, University of Montreal. The course consists of 25 lectures of two hours each, with 10 optional laboratory hours. Part 1, Fundamental Considerations in the Medical and Biological Use of Radioactive Isotopes, deals with physical properties and physical assay of radioactive isotopes; chemical procedures in their analysis; biological procedures; and interpretation of results. Part 2, Review of the Application of Radioisotopes in Medicine and Biology, covers the fields of biochemistry; physiology; clinical diagnosis in internal medicine; surgery; pathology; microbiology and immunology; hygienic aspects of exposure to radiation; therapeutic application; and atomic warfare.

The lectures are given each Tuesday at 8 p.m. in Classroom A of the Medical Building. Further details may be obtained from the Department of Investigative Medicine (Dr. J. S. L. Browne) or the Extension Office, McGill University.

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MEDICAL NEWS *in brief*

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BULLETIN OF POLISH MEDICAL HISTORY AND SCIENCE

The first number (July 1956) of a new journal entitled *Polish Medical History and Science Bulletin* has appeared. The aims of this bulletin appear to be two in number: (1) to present papers on the history of Polish medicine, a field which is relatively unstudied on this continent; (2) to present a conspectus of present-day medical science in Poland. The first number contains three original articles. One is a study of Copernicus as a physician and a humanitarian, the second is a scientific paper on electrophoresis in liver diseases, and the third is an appreciation of Dr. Zalewski, the doyen of Polish otolaryngology, who died recently. The remainder of the issue contains a large number of brief abstracts from the Polish medical literature, followed by a listing of titles of articles published in Polish medical journals and evidently considered of lesser interest. The journal is in the hands of a board of editors, most of whom are in the United States, and is published from 2424 North Kedzie Boulevard, Chicago 47, Illinois.

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ADVERSE REACTIONS TO MEPROBAMATE

Meprobamate is a drug that has received extremely widespread acceptance by the medical profession in the United States as well as by the general public. Since it has been highly praised as a tranquillizing drug, it is well to note the occasional appearance of toxic or allergic reactions to the drug. Friedman and Marmelzat of Beverly Hills, California, *(J. A. M. A.*, 162: 628, 1956) record seven cases in which side-effects appeared. In five cases there were skin lesions, chiefly but not entirely purpuric in nature, very itchy and on one occasion appearing two or three hours after the taking of a single tablet. The rash tends to appear first in the pelvic girdle area, genitalia and groins. It soon clears on stopping the drug. Other reversible side-effects recorded are intestinal hyperperistalsis with rice-water stools, and palsy of the extra-ocular muscles with double vision. Also in three cases paradoxical excitement occurred. It may be that the skin reactions are due to previous sensitization with a similar drug.

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A HYDANTOIN DERIVATIVE IN TREATMENT OF OBESITY

In a mental hospital in Germany, 34 patients, all of whom were markedly overweight, and eight obese normal persons were given a trial of methyldibromostyrylhydantoin (Pesomin), a drug said to reduce appetite and also induce a qualitative change in appetite. Tablets containing 0.27 g. of the drug were given on the following schedule: one tablet daily for the first week, two tablets daily for the second week, three tablets daily for the third week and two tablets three times a day from the fourth week on as continued medication. Treatment con-

tinued usually for three months at least. No change was made in food offered or in other factors. All subjects lost weight (average loss 6 kg. or approximately 13 lb.). The commonest side-effect of the drug was a rash, which appeared in seven cases. General malaise and nausea appeared in five cases and a leucopenia was not uncommon.

The action of the drug is thought to be on the central nervous system. A qualitative change in appetite from foods rich in carbohydrate and fat to vegetables and fruits was observed, unaccompanied by quantitative change.—Tramer and Walther-Buel, *Deutsche med. Wchnschr.*, 81: 1610, 1956.

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AMERICAN HEART ASSOCIATION AWARD FOR RESEARCH

The American Heart Association announces that the 1956 Albert Lasker Award for distinguished achievement in the field of cardiovascular research has been given to Dr. Louis M. Katz of Chicago. Dr. Katz has been Director of the Cardiovascular Research Department, Medical Research Institute, Michael Reese Hospital, Chicago, since 1930. In the citation for the award, it is stated that Dr. Katz has rejected the notion that atherosclerosis is a necessary concomitant of the aging process. He has advanced the thesis rather that experimental atherosclerosis is basically a metabolic disease which is both preventable and reversible.

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MEDICAL STUDENTS CRITICIZE THEIR TEACHING

An editorial in our contemporary, *l'Union Médicale*, comments on the criticism of medical schools by the student body. The editor believes that the student is well placed to judge the quality of his instruction, and to point out gaps in the latter. He refers to a document drawn up by students of the Faculty of Medicine of the University of Montreal, in which they have made certain suggestions for the improvement of their course. The first criticism that they make is that the medical course is not adjusted to the proper training of competent general practitioners, but more to those looking towards specialization. There is too much insistence on diagnosis by laboratory tests and by technical methods; there is also a neglect of problems of a psychological nature which are intimately associated with the daily work of the family doctor. It is suggested that the teaching of the basic sciences and also of the clinical specialties is too compartmented and that the courses are not co-ordinated with a view to producing a unified medical science applicable in all circumstances outside the hospital environment. The students would wish to have some advice on the general management of medical practice and on medical economics. A preference is voiced for more group discussions and for preceptorship under the guidance of a general practitioner.

The students also criticized the relative lengths of their stay in

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various departments, citing this as an instance of the lack of coordination. None of these criticisms is new. Faculties must be well aware of these imperfections and equally well aware of the financial and other obstacles to their correction. Nevertheless, it is well to keep in mind the existence of these problems.

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INTERNATIONAL SYMPOSIUM ON IRON IN CLINICAL MEDICINE

An International Symposium on Iron in Clinical Medicine is planned for January 28 and 29, 1957, at the University of California Medical Center in San Francisco. Several authorities will discuss such topics as iron metabolism—basic principles, iron in pædiatrics, iron deficiency anæmia, and abnormal iron metabolism. The two-day symposium is presented by the University of California Medical Center and Medical Extension together with the Children's Hospital of San Francisco. Participants will include experts from England, Germany and Sweden and from several American universities and medical centres. Ample time will be given to a review of current research concepts, although the orientation of the symposium is primarily clinical. Specific problems in the various specialties will be dealt with.

The session on basic principles of iron metabolism will include talks on etiology of iron deficiency anæmia; iron transport; iron storage — ferritin; transplacental iron and iron kinetics. Iron requirements, problems of the premature, iron absorption in infants, acute iron toxicity, and parenteral iron therapy will be dealt with in the session on iron in pædiatrics. That on iron deficiency anæmia will include discussions of pharmacology of parenteral iron preparations, treatment of iron deficiency anæmia, iron deficiency anæmia of pregnancy, and parenteral iron in pregnancy and menorrhagia. Abnormal iron metabolism will cover such topics as aspects of copper metabolism in human subjects, anæmia of rheumatoid arthritis, other etiological factors, and hæmosiderosis vs. hæmochromatosis.

Further information and application for enrolment may be obtained by writing to Dr. Weymour M. Farber, Head, Medical Extension, University of California Medical Center, San Francisco 2, California.

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EXHIBITION OF MEDICAL PRINTS

Canada will soon have a chance to view a unique collection of medical prints by Rembrandt, Daumier, Hogarth, Toulouse-Lautrec and other great masters. Entitled "Ars Medica", or the Healing Arts, the collection is composed of 85 famous and rare pieces of graphic art depicting the practice of medicine over the centuries. Owned by the Philadelphia Museum of Art, the exhibition is being presented by Smith Kline & French, under whose grant the collection was assembled. After an extended tour of the United States, where it received wide acclaim by both the critics and the general public, "Ars Medica" will now be shown in Canada for the first time. The collection had its official opening at the Montreal Museum of Fine Arts on November 7 and from there will travel to Ottawa, Kingston, Toronto, Winnipeg, Saskatoon, Edmonton, Vancouver and return east to Halifax and Quebec.

Assembled by Carl Zigrosser, Curator of Prints at the Philadelphia Museum, "Ars Medica" is the first collection of its kind. It is being displayed in 15 mobile units which are especially designed for a cross-country tour of this type.

Among the outstanding prints in the collection are Vesalius' "Ninth Plate of Muscles"; Rembrandt's "Portrait of Dr. Ephraim Bonus"; Bellini's "Visit to the Plague Patient"; Winslow Homer's Civil War portrayal of the "Surgeon at Work During an Engagement"; Hogarth's "The Company of Undertakers"; Toulouse-Lautrec's lithograph of the sick French Premier Carnot.

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"The value of an article in a medical journal or in a textbook is due not merely to the information it contains, but also to the ideas which it may inspire."

—Sir Frederick Banting